Contents

Imidazopyridines: 1- and 3-Deazapurines

YURIY M. YUTILOV

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Preface

Volume 89 of Advance in Heterocyclic Chemistry consists of four chapters. The volume commences with an overview of 5,6-dihydroxyindoles and the corresponding diones authored by M. D'Ischia, A. Napolitano and A. Pezzella (University of Naples, Italy), E. J. Land and C. A. Ramsden (Keele University, UK) and P. A. Riley (Mount Vernon Hospital, UK). These compounds play essential roles in the biosynthesis of melanins, the ubiquitous pigments of hair and many other body parts of all mammals including humankind.

"Syntheses, Structures and Interactions of Heterocalixarenes" written by S. Kumar, D. Paul and H. Singh (Guru Nanak Dev University, India) describes the recent significant progress in our understanding of heterocyclic derivatives of calixarenes and in particular their role as receptors in molecular complexes.

Our ongoing series on heterocyclic organometallic complexes, authored by A. P. Sadimenko (University of Fort Hare, South Africa), continues with an account of analogues of pyridine in which the nitrogen is replaced by a boron or a metalloid of the silicon or phosphorus group. This field is exploding with X-ray investigations now confirming many novel structural types.

The volume closes with Y. M. Yutilov's (Litvinenko Institute, Donetsk, Ukraine) survey of 1- and 3-deazapurines, two important classes of imidazopyridines.

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5,6-Dihydroxyindoles and Indole-5,6-diones

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I. Introduction

Among naturally occurring indoles, the 5,6-dihydroxyindoles occupy a special position because of their central role in the biosynthesis of melanins (Scheme 1). The melanins are the most prominent pigments in man and non-human mammals, and are the main constituents of the black ink that cephalopods discharge when frightened. Credit for the discovery of the 5,6-dihydroxyindole system goes to H.S. Raper who, in 1927, obtained 5,6-dihydroxyindole **1** and 5,6-dihydroxyindole-2-carboxylic acid **2**, as the methyl ethers, by oxidation of L-tyrosine with tyrosinase after reduction of the mixture in the early stages (27BJ89). This seminal work was a landmark in the history of melanin research and paved the way for a series of studies carried out mainly in Naples and in the United Kingdom, and aimed at elucidating the chemistry of 5,6-dihydroxyindoles.

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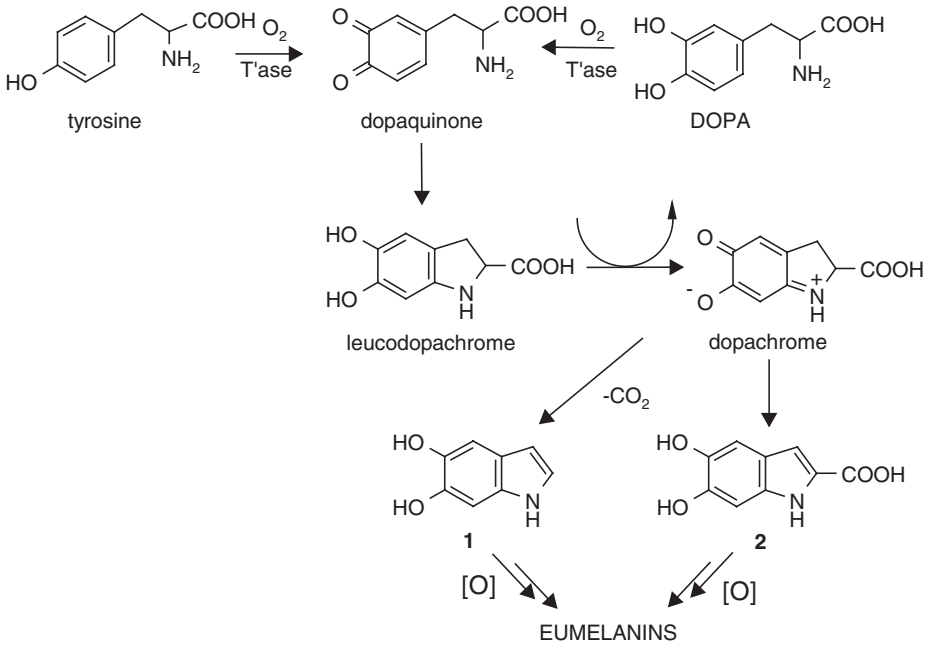


Scheme 1

The first synthesis of the indoles **1** and **2** was described in 1948 (48JCS2223), and preliminary insights disclosed their remarkable facility to oxidation. In the subsequent three decades, studies of 5,6-dihydroxyindoles were largely focused on chemical and biomimetic synthesis by oxidative cyclization of 3,4-dihydroxyphenylethylamines, and very little progress was recorded on the study of their oxidative chemistry. Despite considerable efforts, reviewed by Nicolaus, Thomson and Swan (68MI1, 78MI190, 74AC305, 74FCON522), insights into the nature of the black insoluble materials produced by oxidation of the 5,6-dihydroxyindoles **1** and **2** were thwarted by their intractable nature and the lack of well defined physical and spectral characteristics. In fact, during the 1960s and 1970s very few organic chemists dared venture into such a perilous field of research, and the brave investigators were invariably discouraged by the bewildering complexity of the reaction mixtures. This state of affairs is well illustrated by just two lines being dedicated to 5,6-dihydroxyindole **1** in *Rodd's Chemistry of Carbon Compounds* in 1973 (73MI424).

An important event in 1985 that gradually led to reversal of this attitude was the isolation by Prota and his associates of a dimer of indole **1** and this provided the first insight into the mode of polymerization of this indole. Since then, literature on 5,6-dihydroxyindoles has grown significantly and so has our knowledge and appreciation of the field. Several reports on the occurrence of 5,6-dihydroxyindole **1** and a series of 5,6-dihydroxyindole-containing systems in natural sources (e.g. 96NPL137, 01ZN714, 02JOC6671) and their increasing exploitation as active ingredients for

dermocosmetic formulations contributed to reinforcing this trend. Although several excellent reviews and book chapters are available, coverage of the topic has usually been framed in the context of melanogenesis (74AC305, 74FCON522, 78MI190, 80JID122, 80PA223) and as a result several aspects of the chemistry of this intriguing class of heterocycles have never been addressed in a systematic manner.

This chapter aims at filling this gap. It is aimed at covering the chemistry of 5,6-dihydroxyindoles up to the end of 2004, and exemplifies in its authorship the long tradition of the Neapolitan and English schools of organic chemistry in the field. The focus is naturally on the 5,6-dihydroxyindoles (e.g. **1** and **2**), but other indoles are also considered because of their structural analogy and conceptual relevance. These include 2,3-dihydro-5,6-dihydroxyindoles, 2,3-dihydroindole-5,6-diones (usually referred to as aminochromes) and 1*H*-indole-5,6-diones. Quite unprecedented is the latter section, which represents the first systematic review of the chemistry of 1*H*-indole-5,6-diones, a class of compounds that until a few years ago belonged to the realm more of conjectures than of direct experimental evidence. Whenever appropriate, an historical perspective of the field will be presented, with the dual scope of keeping due records of the early papers that laid the foundations of 5,6-dihydroxyindole chemistry and providing the reader with the necessary background to appreciate conceptual and technological advances. For further information and early studies the reader is referred to several reviews (74FCON522, 76END32, 80PA223, 80JID122, 95MI94, 01JPP(B)123), the book on Melanins and Melanogenesis by Giuseppe Prota (92MI1), and book chapters (74MI1104, 98MI307, 05MI3).

II. 5,6-Dihydroxyindoles

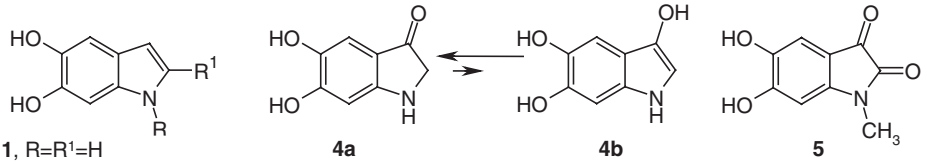
A. Physical Properties

1. *General Properties*

The 5,6-dihydroxyindoles, including the parent system **1**, are usually white-to-grey crystalline solids that melt with extensive decomposition and darkening. They are soluble in alcoholic solvents and acetone, less in acetonitrile, ethyl acetate, dimethyl sulphoxide (DMSO), tetrahydrofuran (THF), and water, and only sparingly soluble in hydrocarbons, e.g. benzene and light petroleum. A detailed physicochemical characterization of compound **1** was described by Murphy and Schultz (85JOC5873) (85JOC2790). The pK_a values for the first and second ionizations of indole **1** were determined as 8.9 and >10.2, respectively. 5,6-Dihydroxy-1-methylindole **3** has pK_a values of 8.4 and 10.7 in water.

A characteristic subgroup of 5,6-dihydroxyindoles is represented by the 3,5,6-trihydroxyindoles (e.g. **4b**), also known as 5,6-dihydroxyindoxyls or "lutins", which exist almost exclusively in the 3-keto form (i.e. **4a**). These are crystalline solids which form deep-yellow solutions in water and exhibit a typical intense green fluorescence that has provided the basis of several tests for catecholamines in biological fluids (59CR181). When pure, both anhydrous 3,5,6-trihydroxy-1-methylindole **4**

(adrenolutin) and the monohydrate are bright-yellow crystalline solids, slightly soluble in water and in polar solvents. Aqueous solutions rapidly turn dark in air with loss of fluorescence. 5,6-Dihydroxy-2,3-dihydro-1-methylindole-2,3-dione **5** (5,6-dihydroxy-1-methylisatin) is a brick-red solid (88T6441).



2. *Ultraviolet Spectroscopy*

The UV spectral data of several 5,6-dihydroxyindoles are summarized in Table 1.

3. *NMR Spectroscopy*

The ^{1}H-NMR properties of 5,6-dihydroxyindole **1** and some of its derivatives are reported in Table 2 and ^{13}C-NMR data are collected in Table 3.

4. *Mass Spectrometry*

The EI–MS spectrum of 5,6-dihydroxyindole **1** displays a molecular ion at m/z 149, with fragmentation peaks denoting loss of H_2O (m/z 131), HCN (m/z 120) and H_2O/CO (m/z 103) (85JOC2790).

Table 1. Ultraviolet spectral data for 5,6-dihydroxyindole derivatives

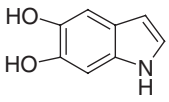
Compound	Solvent	λ_{max} (ε) (nm)	References
5,6-Dihydroxyindole	EtOH	302 (6110), 275 (3970)	65JHC387
5,6-Dihydroxyindole	Water	296 (log ε 3.52)	85JOC2790
5,6-Dihydroxyindole-2-Carboxylic acid	MeOH/1M HCl	320 (17700)	74BJ207
3,5,6-Trihydroxy-1-methylindole	Water	220, 255, 285, 410	59CR181
5,6-Dihydroxy-1-methylisatin	Water	509 (log ε 3.42), 363 (log ε 3.91)	88T6441
5,6-Dihydroxy-2,3-dimethylindole	EtOH	229, 289	49JCS2061

Table 2. Chemical shifts of protons in 5,6-dihydroxyindole derivatives

Compound	Solvent	δH-2	δH-3	δH-4	δH-7	References
5,6-Dihydroxyindole	$CDCl_3$	6.98	6.20	6.89	6.82	85JOC2790, 89JOC5190
5,6-Dihydroxyindole	$(CD_3)_2CO$	7.06	6.23	6.98	6.89	99SYN793
5,6-Dihydroxyindole-2-Carboxylic acid	DMSO-d_6		6.81	6.85	6.76	96T7913
5,6-Diacetoxy -1-methyl indole	$CDCl_3$	7.06	6.44	7.37	7.14	93JOC1607
3,5,6-Trihydroxy-1-methylindole	DMSO-d_6	3.58		6.70	6.33	88T6441
5,6-Dihydroxy-1-methylisatin	CD_3OD			6.96	6.47	88T6441
5,6-Diacetoxy -2-methyl indole	$(CD_3)_2CO$		6.14	7.18	7.11	93T9143
5,6-Diacetoxyindole	DMSO-d_6	7.41	6.45	7.36	7.27	03SL1853, 85JOC5873
5,6-Diacetoxyindole	$(CD_3)_2CO$	7.33	6.43	7.32	7.23	99SYN793
5-Hydroxy-6-methoxyindole	$CDCl_3$	7.08	6.42	7.15	6.87	87JHC941
6-Hydroxy-5-methoxyindole	$CDCl_3$	7.05	6.45	7.09	6.96	87JHC941
5,6-Dihydroxy-4,7-dimethylindole	DMSO-d_6	7.0	6.20			82JMC263

5. *Computational Studies*

Although the exact structure of eumelanin has still not been determined, there is strong evidence that it has a polymeric structure built up of 5,6-dihydroxyindole **1**, 5,6-indolequinone **6** and semiquinone **7** monomers. Eumelanin has exceptionally good photoprotective properties and an absorption spectrum spanning a large part of the solar spectrum. These special properties have prompted a number of theoretical studies of 5,6-dihydroxyindoles, their oxidation products and dimers, and oligomeric models of eumelanin.



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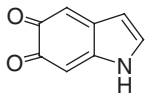

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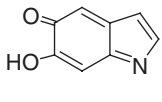

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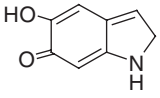

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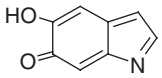

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Table 3. Chemical shifts of carbons in 5,6-dihydroxyindole derivatives

Compound	Solvent	δC-2	δC-3	δC-4	δC-5	δC-6	δC-7	δC-8	δC-9	References
5,6-Dihydroxyindole	$CDCl_3$	122.77	101.31	104.87	130.65	140.55	98.66	142.35	120.96	85JOC2790
5,6-Dihydroxyindole-2-Carboxylic acid	DMSO-d_6	126.13	107.43	105.27	142.32	146.46	97.29	132.97	120.22	96T7913
5,6-Diacetoxy-1-methyl indole	$CDCl_3$	131.2	102.1	114.9	134.8	136.8	104.3	138.5	126.8	93JOC1607
3,5,6-Trihydroxy-1-methyl indole	DMSO-d_6	60.96	195.61	106.96	156.05	160.05	95.89	139.16	112.74	88T6441
5,6-Dihydroxy-1-methyl isatin	CD_3OD	163.57	177.21	107.40	149.60	161.22	98.12	142.73	104.24	88T6441
5,6-Diacetoxy -2-methyl indole	$(CD_3)_2CO$	134.34	100.45	113.09	137.00	138.07	105.48	137.96	127.40	93T9143
5,6-Diacetoxyindole	DMSO-d_6	127.55	101.56	113.75	136.28	137.84	106.12	133.52	125.59	03SL1853
5-Hydroxy-6-methoxyindole	$CDCl_3$	123.61	101.33	104.69	142.05	145.61	94.81	130.83	122.09	87JHC941
6-Hydroxy-5-methoxyindole	$CDCl_3$	122.64	101.45	102.18	143.14	142.80	96.36	130.50	120.38	87JHC941

In 1960, Longuet–Higgins suggested that melanins might act as intrinsic semiconductors (60ABB231) and this proposal was supported by Hückel calculations on monomers (61BBA384). Subsequently, this simple Hückel model was rejected (64BJ471), but later a more sophisticated Hückel analysis of long oligomers was shown to be compatible with melanin EPR data (88JCP4088, 90JCP2630, 90JCP2848). Recently, with the advent of much more accurate computational methods, there have been a number of detailed theoretical investigations of the indole monomers and dimers, and also oligomeric models of eumelanin.

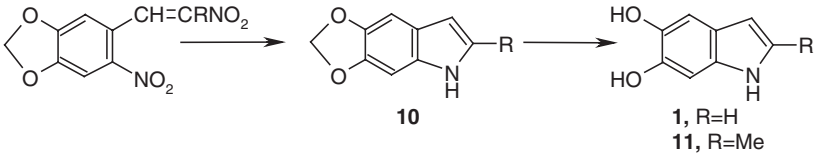
Using B3LYP and PBE0 calculations the relative stabilities and the excitation energies of the tautomers of 5,6-dihydroxyindole and 5,6-indolequinone have been investigated (03JPC(B)7162). For 5,6-dihydroxyindole the most stable structure was **1** in both the gas phase and aqueous solution. In aqueous solution the quinone methide **8** was calculated to be the next most stable tautomer. In the gas phase the indolequinone **6** was calculated to be in equilibrium with the quinone methide **9**, but in polar solvents the quinone methide concentration was calculated to be negligible. Interestingly, these calculations suggest that the tautomer **7** is not present in the gas phase or aqueous solution, although this isomer is frequently referred to in the interpretation of experimental data.

An *ab initio* and semi-empirical study of the species **1**, **6** and **7** and their ions has shown that these molecules can all behave as electron acceptors (99JPC(B)2993). The calculated geometries were tabulated and calculated optical absorption properties compared with those of eumelanins. The authors conclude that the electronic properties are consistent with the semiconductor model proposed for melanins (60ABB231). Density functional theory (DFT) calculations on the monomers **1**, **6** and **7** and several dimers (03JPC(B)3061) gave calculated properties in good agreement with those of the *ab initio* study (99JPC(B)2993) and with experimental data. These DFT studies were then extended to calculations of higher oligomers (03JPC(B)11558) and the calculated oligomeric spectra provide support for a structural model of eumelanin (94PCR263, 94JVST(B)1512).

A first-principles DFT study of the monomers **1**, **6** and **7** has calculated electronic and vibrational properties and has focused attention on the HOMO–LUMO gap, which is twice as large in the dihydroxyindole **1** as in the quinone **6** and semiquinone **7** (04JCP8608). The authors suggest that this may be significant in understanding the broadband optical absorption of eumelanins. A semi-empirical INDO study has examined the electronic properties of stacked eumelanin monomers and the results suggest localization of charge on the monomer subunits and an electron hopping mechanism for electron transfer (03CPL532).

B. Preparation

Strategies for the preparation of 5,6-dihydroxyindoles involve (i) multistep approaches based on the extension and refinement of conventional indole syntheses or (ii) biomimetic-type approaches based on conversion of appropriate biosynthetic precursors, i.e. catechol amines and aminochromes, as well as related compounds. Although these approaches have been pursued in parallel, they offer a convenient



Scheme 2

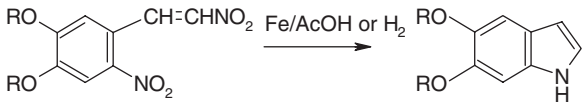
conceptual framework for coverage of the topic and will therefore be dealt with separately. To permit appreciation of the main advances within each approach, a chronological survey of the literature is presented. More recently, reports describing preparations of 5,6-dihydroxyindoles have included a significant number of patents in which several practical applications of these advances were disclosed.

Since strategies for the multistep synthesis of indole **1** and indole-2-carboxylic acid **2** are usually based on different schemes, a detailed discussion of the synthesis of compound **2** and related indole-2-carboxylic acid derivatives is covered separately in Section IIB2.

1. *Multistep Syntheses Based on Conventional Procedures: 5,6-Dihydroxyindole **1** and Related Compounds*

Early multistep approaches to 5,6-dihydroxyindole **1** and related derivatives were based on the reductive cyclization of 2,β-dinitro-4,5-dihydroxystyrenes. The first synthesis was developed in 1948 by Burton and Duffield (48NAT725) and involved the condensation of piperonal with nitromethane followed by nitration in acetic acid to give 2,β-dinitro-4,5-methylenedioxystyrene which on reduction afforded 5,6-methylenedioxyindole **10** (R = H) (Scheme 2).

Similarly, β-nitro-β-methyl-3,4-methylenedioxystyrene (from piperonal and $EtNO_2$) was nitrated to 2,β-dinitro-β-methyl-4,5-methylenedioxystyrene, which was reduced to 5,6-methylenedioxy-2-methylindole **10** (R = Me) (48JCS2223, 49JCS78, 50JA1062). Deprotection of the indoles **10** was effected with pyridine-HCl to give dihydroxyindoles **1** and **11** in poor yield. In the same year, Beer and co-workers (48NAT525) reported a synthesis of compound **1** based on a variant of an earlier synthesis of 5-hydroxyindole. This approach involved reduction of 4,5-diacetoxy-2,β-dinitrostyrene with Fe powder and AcOH and subsequent deacetylation of the resulting 5,6-diacetoxyindole **12** (R = Ac) (Eq. (1)). In this work, the ease of oxidation of 5,6-dihydroxyindoles in slightly alkaline solution to give melanin-like products was underscored.



R=Ac, Me

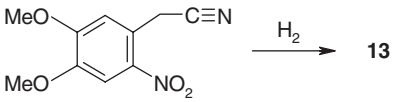
12, R=Ac
13, R=Me

(1)

An interesting aside to these early synthetic efforts is the preparation of 5,5′,6,6′-tetrahydroxyindigo by reaction of 2-nitro-4,5-bis (methoxymethoxy) benzaldehyde

with acetone in the presence of 10% NaOH, to give 5,5′,6,6′-tetrakis(methoxymethoxy)indigo, which heated in acid gave the indigo as a black monohydrate (48JCS1244).

During the early 1950s, the synthesis of 5,6-dimethoxyindole **13** was also pursued by catalytic hydrogenation of 4,5-dimethoxy-2,β-dinitrostyrene (Eq. (1)) (53JA5887) and by an alternative approach (55JA3844) involving low-pressure hydrogenation of 4,5-dimethoxy-2-nitrophenylacetonitrile (Eq. (2)). 2-Aminoindoles are probably intermediates in the hydrogenation of these nitronitriles. Using this and related approaches (56JA3698), several substituted 5,6-dimethoxyindoles were prepared, including 5,6-dimethoxyoxindole:



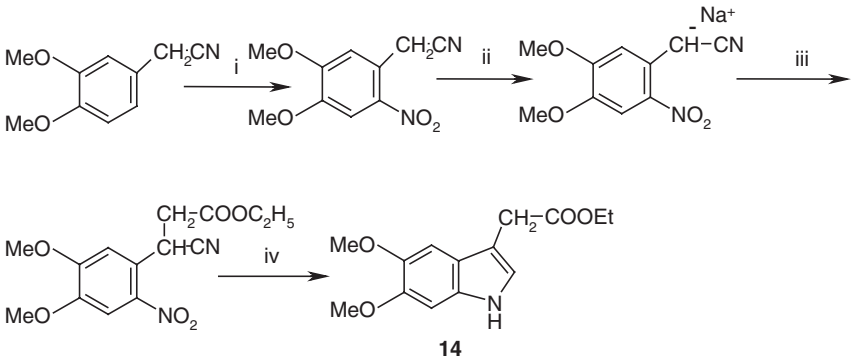
(2)

In an extension of these studies (55JA3844), the synthesis of 5,6-dimethoxyindole-3-propionic acid was achieved by reductive cyclization of 3-cyano-3-(2-nitro-4,5-dimethoxyphenyl) propanoate esters with H_2 over 10% Pd/C in ethyl acetate. This approach was later revisited for the preparation of ethyl 2-(5,6-dimethoxyindol-3-yl)acetate **14** (80SYN663) (Scheme 3).

The dinitrostyrene approach has also been applied to the preparation of 5,6,7-trimethoxyindole by reductive cyclization of 2-nitro-3,4,5-trimethoxy-β-nitrostyrene, obtained by the nitration of 3,4,5-trimethoxy-β-nitrostyrene in Ac_2O with fuming HNO_3 (57JOC331).

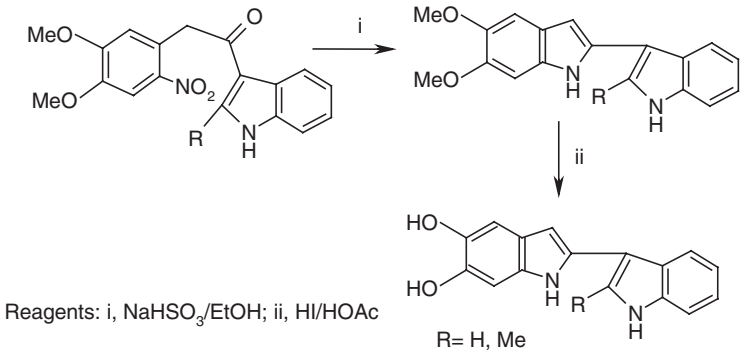
5,6-Dihydroxy-2,3′-biindolyls have been synthesized via reductive cyclization of substituted 3-(*ortho*-nitrophenylacetyl)indoles followed by demethylation of the resulting 5,6-dimethoxy-2′-methyl-2,3′-biindolyl and 5,6-dimethoxy-2,3′-biindolyl with HI (62JOC507) (Scheme 4).

A synthesis of adrenolutin **4** (53HCA708) has also been described and involves thermal cyclization at 240 °C of ethyl (3,4-isopropylidenedioxyanilino)bromomalonate to ethyl 5,6-isopropylidenedioxyindoxyl-2-carboxylate as the key step (Scheme 5).

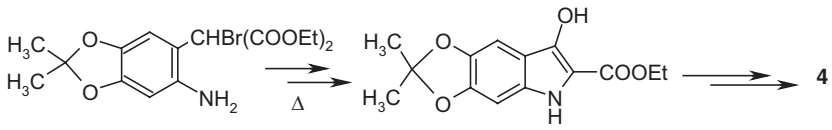


Reagents: i, HNO_3/AcOH/Ac_2O; ii, NaH/DMF;iii, Br-CH_2-$COOC_2H_5$;iv, Pd/C/H_2

Scheme 3



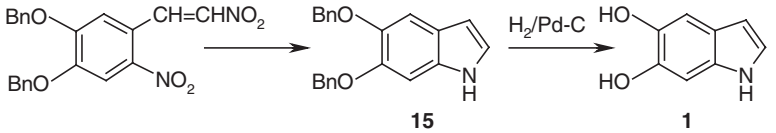
Scheme 4



Scheme 5

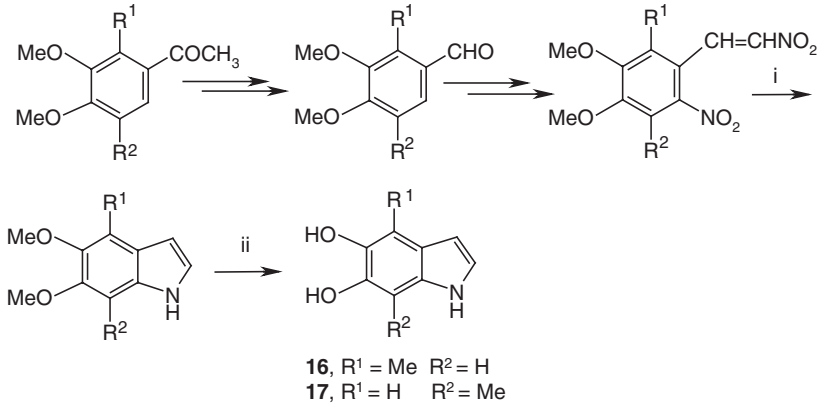
Despite some improvements, these procedures remained of very limited preparative value, as they suffered from several drawbacks relating to the final cyclization and deprotection steps, in which the products are partially degraded. In 1965, the 6,β-dinitro-4,5-dihydroxystyrene approach to 5,6-dihydroxyindole **1** was revisited and converted into a synthetic sequence of practical value for the gram scale preparation of compound **1** and its derivatives. In this method (Scheme 6), worked out by Benigni and Minnis (65JHC387), the main advancement stemmed from the introduction of the benzyl protecting group. After a chromatographic step on an alumina column to purify the resulting 5,6-dibenzyloxyindole **15**, the synthesis was concluded by efficient deprotection using catalytic hydrogenation over Pd/C giving virtually pure 5,6-dihydroxyindole **1**. The success of this approach also arises from the regioselective nitration of the intermediate β-nitro-3,4-dibenzyloxystyrene, giving exclusively the *ortho*-nitro derivative (2,β-dinitro-4,5-dibenzyloxystyrene). This paper (65JHC387) represents a milestone in the synthesis of 5,6-dihydroxyindoles and provided the opportunity for further advances in the field of melanogenesis based on investigations of the chemistry of 5,6-dihydroxyindole **1** and its congeners. Preparation of the indole **15** by this approach has recently been exploited in the synthesis of 5,5′,6,6′-tetrahydroxy-3,3′-biindolyl (04T60).

In the 1980s, a series of papers re-awakened interest in the synthesis of 5,6-dihydroxyindoles. In the first of these papers (82JMC263) indole **1** and its 4- and 7-methyl derivatives **16** and **17** were synthesized and evaluated for their ability to inactivate catechol-*O*-methyl transferase. The synthetic scheme employed for the methylated derivatives was based on the dinitrostyrene approach starting from an appropriate acetophenone derivative (Scheme 7). The acetophenones were converted



15 1

Scheme 6



16, R^1 = Me R^2 = H
17, R^1 = H R^2 = Me

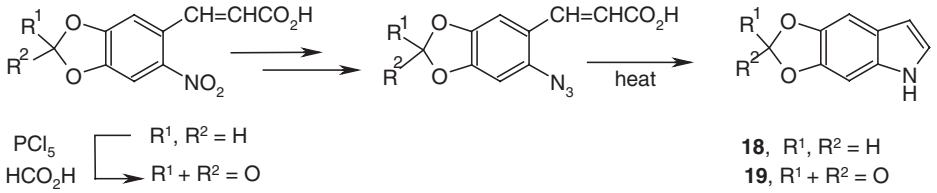
Reagents: i, Fe/HOAc; ii, HBr, Dowex

Scheme 7

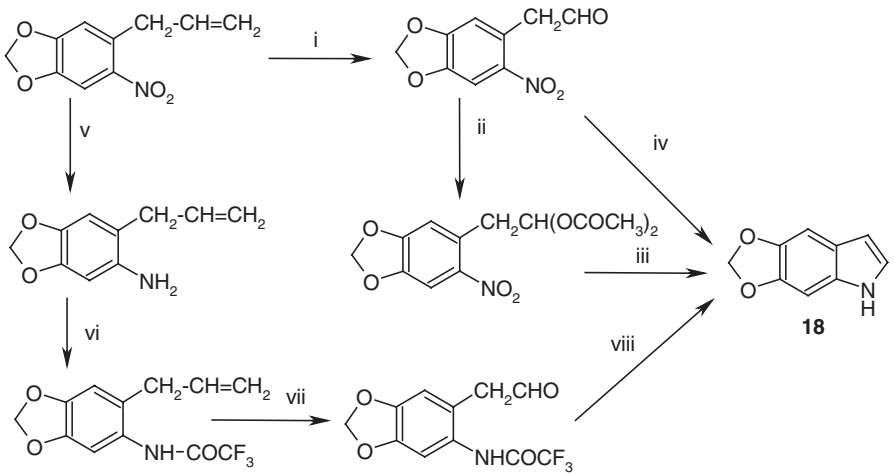
to the corresponding 3,4-dimethoxybenzaldehydes by a three-step sequence involving oxidation to the acid, reduction to the alcohol and controlled oxidation with pyridinium chlorochromate. Henry condensation with $MeNO_2$, ring nitration (fuming HNO_3) and reductive cyclization (Fe/HOAc) led eventually to 5,6-dimethoxy-4-methylindole and 5,6-dimethoxy-7-methylindole which were converted to indoles **16** and **17** by treatment with 48% HBr followed by neutralization with ion-exchange resin (Dowex-2). In this scheme, product yields for the cyclization and deprotection steps were no better than 37%.

A substantial improvement of the reductive cyclization of dimethoxy or dibenzyloxydinitrostyrene derivatives was reported by the same group (83JOC3347). They showed that when a mixture of the alkoxydinitrostyrene, Fe and HOAc is heated under reflux in a non-polar solvent system (benzene-cyclohexane or toluene) in the presence of silica gel (column chromatography grade, 70–270 mesh) the reaction is complete in less than 1 h and the corresponding alkoxyindoles are obtained in a high state of purity with dramatic improvements in yields (around 90%).

Another study (84JHC1183) was prompted by the value of ester derivatives as storable but ready sources of 5,6-dihydroxyindole **1** for biological studies (67NAT190) (67JPS1019), and focused on the synthesis of the cyclic carbonate derivative **19** (Scheme 8). This procedure starts from 3,4-methylenedioxycinnamic acid and utilizes thermal decomposition of an azide intermediate, produced from a



Scheme 8



Reagents: i, O_3,CH_3OH; ii, $(Ac)_2O$; iii, H_2, Pd/C, CF_3CO_2H; iv, $Na_2S_2O_4$; v, $SnCl_2$/HCl; vi, $(CF_3CO)_2O$; vii, O_3,CH_3OH; viii, $HN(CH_2CH_2NH_2)_2$

Scheme 9

nitrated precursor via diazonium salt chemistry. The whole synthetic procedure relies on the hydrolytic propensity of the cyclic carbonate ring and problems arise from the formation of brownish-black materials in the last step. This is partly circumvented by the use of copper powder. The scheme was successfully extended to the preparation of 5,6-methylenedioxyindole **18**, for which alternative synthetic routes have also been described (Scheme 9) (84JHC1183).

An alternative route involves ozonolysis of 6-nitrosafrole followed by reductive conversion to an aldehyde which is converted into indole **18** by reduction, with or without prior conversion to a *gem*-diacetate (Scheme 9). Alternatively, 6-nitrosafrole can be reduced to the corresponding amine which is trifluoroacetylated, ozonized and allowed to cyclize by removal of the protecting group with diethylene triamine (86% yield of **18**). This latter step is particularly clean, high yielding and easy to work up.

Another study (86SC267) reported the formation of 5,6-dimethoxy-1-tosylindole **20**, and the corresponding indoline, by $Tl(CF_3COO)_3$ oxidation of a sulphonamide precursor (Eq. (3)) to give the radical cations, which undergo rapid intramolecular capture by the toluenesulphonamide group.

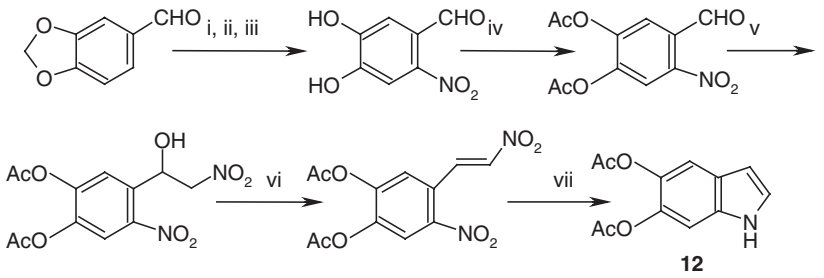
20 (3)

In 1985, a series of papers by American workers refocused attention on the classical dinitrostyrene route to 5,6-dihydroxyindole **1**, exemplified in the Benigni and Minnis synthesis (Scheme 6). Although these papers did not upset the foundations of that synthetic route, they brought to focus and addressed critical issues concerning the role and removal of protecting groups, and the reductive cyclization of dinitrostyrenes.

From previous studies, it was known that aryl or alkyl *O*-protecting groups were essential to achieve *ortho*-nitration of both 3,4-dihydroxy-β-nitrostyrenes and 3,4-dihydroxybenzaldehydes. However, deprotection is usually difficult when carried out as the last step following formation of the 5,6-dihydroxyindole system, since 5,6-dihydroxyindole **1** is unstable under the conditions used for most deprotections. On the other hand, easily removable ester groups direct nitration to the wrong position. In two related communications (85SC321, 85SC423), the utility of the benzyl group for protection of phenolic OH was underscored, and procedures for the facile cleavage of the methylenedioxy and benzyloxyl groups were developed to produce either 4,5-dihydroxy-2-nitrobenzaldehyde or (*E*)-4,5-dihydroxy-2,β-dinitrostyrene as well as the monomethylated derivatives under mild conditions.

Noteworthy is the efficient chemoselective removal of the benzyl groups by refluxing with trifluoroacetic acid under an oxygen-depleted atmosphere. In both papers, the underlying rationale was removal of protecting groups prior to, rather than after, cyclization of the dinitrostyrene. Accordingly, in one paper (85SC321) catalytic hydrogenation over 10% Pd/C was proposed as a mild and efficient method to effect the reductive cyclization of unprotected (*E*)-4,5-dihydroxy-2,β-dinitrostyrene in aqueous dispersion. In an extension of that work (85JOC2790) the cyclization of (*E*)-4,5-dihydroxy-2,β-dinitrostyrene (53–76% yield) was improved by performing the catalytic hydrogenation in MeOH, to limit decomposition of the labile product in the aqueous medium. Evaporation, sonication of the residue in dry dichloromethane and chromatography on silica gave eventually the product in a crystalline form.

In a subsequent paper, an efficient synthetic route to the diacetate **12** (Scheme 10), featuring the preparation and cyclization of (*E*)-4,5-diacetoxy-2,β-dinitrostyrene, was described (85JOC5873). Problems do arise from the unsuitability of the acetyl group for proper orientation of nitration and extensive degradation and side reactions occurring during cyclization. The procedure starts with nitration of piperonal followed by demethylenation with $AlCl_3$ in dichloroethane and subsequent treatment with HBr. This early deprotection step is necessary since (*E*)-4,5-methylenedioxy-2,β-dinitrostyrene is deprotected in low yield. Direct Knoevenagel/Henry condensation of the resulting 4,5-dihydroxy-2-nitrobenzaldehyde with nitromethane is slow and of limited preparative value. This problem, however, is circumvented by conversion into the acetylated derivative. Thus, 4,5-diacetoxy-2-nitrobenzaldehyde reacts smoothly with nitromethane in 2-propanol in the presence

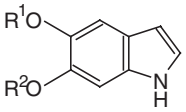


Reagents: i, HNO_3; ii, $AlCl_3$, $ClCH_2CH_2Cl$; iii, HBr; iv, Ac_2O; v, CH_3NO_2, KF; vi, Ac_2O; vii, H_2/Pt/C

Scheme 10

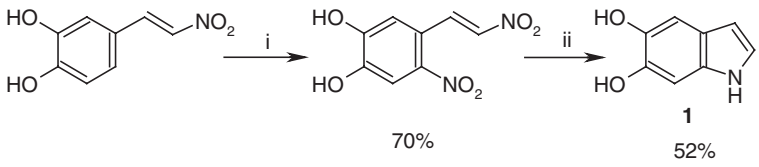
of *N*-methylmorpholine and KF as non-nucleophilic base to give the addition product which is dehydrated with warm acetic anhydride/sodium acetate to provide the desired (*E*)-4,5-diacetoxy-2,*β*-dinitrostyrene in high yield. Reductive cyclization in acetic acid with less than 20 psi H_2 over 5% Pt/C gave compound **12** in up to 73% yield after removal of the solvent and HPLC purification.

This procedure, with slight modifications, was extended to the synthesis of 5-hydroxy-6-methoxyindole **21**, 6-hydroxy-5-methoxyindole **22** and their *O*-acetates (87JHC941). The synthesis of 4-methyl-, 7-methyl- and 4,7-dimethyl-5,6-dihydroxytryptamines from substituted benzaldehydes *via* the corresponding indoles has also been reported (85JMC1273).



21, R^1=H, R^2=Me
22, R^1=Me, R^2=H

In a more recent paper (99SYN793), a significant short-cut to 5,6-dihydroxyindole **1** was achieved using a three-step procedure (Scheme 11) that avoids the use of protecting groups. This method capitalises on the Zn(II)-controlled regioselective nitration of 3,4-dihydroxy-*β*-nitrostyrene with $C(NO_2)_4$ at pH 8.0, in which the metal cation served as labile OH-protecting group directing nitration to the desired 2-position. The other remarkable achievement was the reductive cyclization of the resulting (*E*)-4,5-dihydroxy-2,*β*-dinitrostyrene with $Na_2S_2O_4$ at pH 4 in the presence of Zn(II). The latter addition, to form *in situ* ZnS_2O_4, proved to be essential for product formation. The synthesis was successfully extended to the acetyl and benzyl derivatives and is superior to previous procedures in terms of overall yield (35 vs. 21% for **1** by the Benigni and Minnis procedure), lack of tedious and cumbersome protection/deprotection and purification steps, and suitability for relatively large-scale preparations.



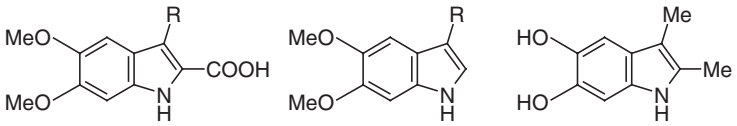
Reagents: i, $C(NO_2)_4$; Zn(II); ii, $Na_2S_2O_4$, Zn(II), pH = 4

Scheme 11

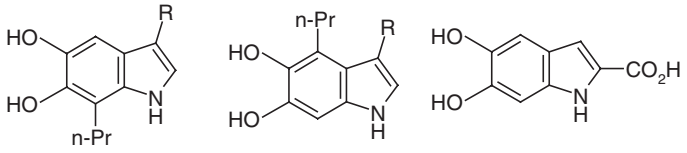
A variant of Scheme 11 has recently been developed for the synthesis of 5,6-diacetoxyindole **12** (03SL1853) and is based on a four-step sequence involving Henry condensation of 3,4-dihydroxybenzaldehyde with nitromethane followed by acetylation, nitration with fuming HNO_3 and Zn(II)-aided reductive cyclization of the dinitrostyrene with $Na_2S_2O_4$ (48% overall yield).

2. *Multistep Syntheses Based on Conventional Procedures: 5,6-Dihydroxyindole-2-Carboxylic Acid* **2** *and Related Compounds*

The first approach to 5,6-dihydroxyindole-2-carboxylic acid **2** and related derivatives was due to Beer and co-workers (49JCS2061) and was based on the reductive cyclization of 2-nitro-4,5-dihydroxyphenylpyruvic acid or a derivative. The critical reduction step is achieved with Fe powder in ethanol/acetic acid. Notably, indole **2** was reported to oxidize poorly and only slowly, giving in the course of 24 h a dark-brown solution but not an insoluble product of the melanin type. This observation led to the conclusion that "… it is unlikely that 5,6-dihydroxyindole-2-carboxylic acid is a precursor of melanin". This conclusion was disproved by subsequent studies (97T8281). In the same paper, the preparations and properties of 5,6-dimethoxy-3-phenyl-2-indolecarboxylic acid **23** (R = Ph), 5,6-dimethoxy-3-methyl-2-indolecarboxylic acid **23** (R = Me), 5,6-dimethoxy-3-phenylindole **24** (R = Ph), 5,6-dimethoxy-3-methylindole **24** (R = Me) as well as that of 5,6-dihydroxy-2,3-dimethylindole **25** were reported.

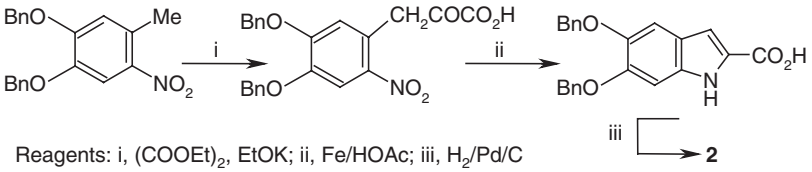


In continuation of their studies on melanin formation, the same authors (51JCS2426) reported the synthesis of 5,6-dihydroxy-7-propylindole **26** (R = H), 5,6-dihydroxy-7-propyl-3-methylindole **26** (R = Me), 5,6-dihydroxy-4-propylindole **27** (R = H), and 5,6-dihydroxy-4-propyl-3-methylindole **27** (R = Me) by alternative routes based on decarboxylation of the corresponding indole-2-carboxylic acids.

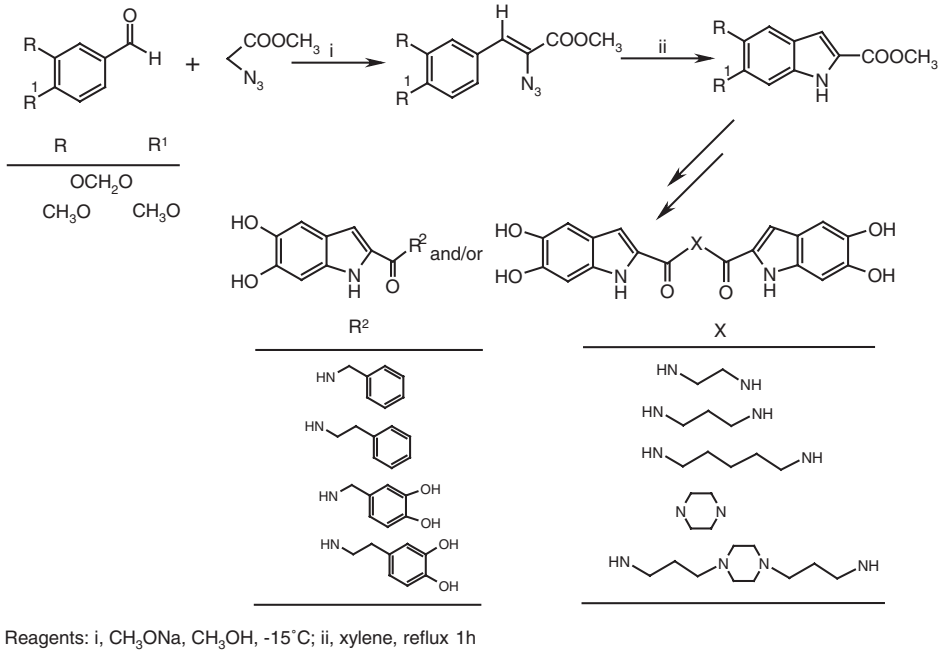


26 **27** **2**

The most practical gram scale synthesis of the acid **2** and related monomethylated derivatives was reported by Benigni and Minnis (65JHC387) (Scheme 12) and involves condensation of 4,5-dibenzyloxy-2-nitrotoluene with diethyl oxalate promoted by potassium ethoxide. Reductive cyclization of the resulting 2-nitro-4,5-dibenzyloxyphenylpyruvic acid with Fe powder in ethanol/acetic acid then leads



Scheme 12



Scheme 13

to 5,6-dibenzyloxyindole-2-carboxylic acid which is readily converted to indole **2** by catalytic hydrogenation on Pd/C (overall yield less than 20%).

Very recently (04MI67), the synthesis and biological evaluation of the acid **2** and derivatives has been reported. Indole **2** was prepared by a synthetic route that hinges on the Knoevenagel/Hemetsberger reaction (70MC161) of dialkoxybenzaldehydes with methyl azidoacetate to give azidocinnamate intermediates which are cyclized to the corresponding indole derivatives by thermal decomposition of the azido group in refluxing xylene (Scheme 13).

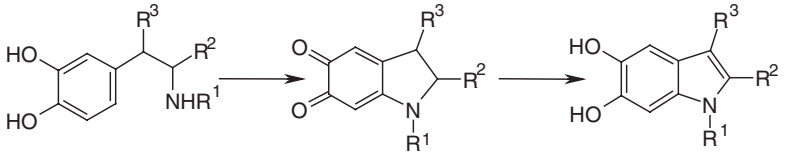
3. *Biomimetic Syntheses of 5,6-Dihydroxyindoles **1** and **2**, and Related Derivatives Based on Oxidative Cyclization of 3,4-Dihydroxyphenylethylamines*

Biomimetic-type syntheses of indoles **1** and **2** are analogous to the early stages of melanogenesis in which a 3,4-dihydroxyphenylethylamine is oxidized to the corresponding *ortho*-quinone. The latter undergoes intramolecular cyclization to give an aminochrome intermediate which is converted into the indole product (Scheme 14).

Within this scheme fall several variants in which the aminochrome precursors **28** are obtained by different approaches. Usually, biomimetic syntheses have been utilized for the rapid preparation of up to hundreds of milligrams of pure indoles but are hardly amenable to substantial scale-up, mainly because of the limited solubility of the substrate, the limited efficiency of the cyclization step and the competition with intermolecular processes becoming predominant at higher concentrations and interfering with the synthesis.

To avoid repetitions or overlaps with the following sections, coverage of the topic will be restricted to those papers in which the emphasis is on 5,6-dihydroxyindole preparation. For a discussion of the preparation of the indoline and aminochrome precursors see Sections IIIB and IVB.

The foundations of these biomimetic-type syntheses were laid by the Raper–Mason scheme of melanogenesis and are outlined in a series of seminal papers by Raper (27BJ89) and Mason in 1948 (48JBC83) dealing with the mechanism of oxidation of 3,4-dihydroxyphenylalanine (dopa) by tyrosinase or chemical agents. Oxidation of dopa with tyrosinase or Ag_2O led to dopachrome (Scheme 1) which was left to rearrange at pH 5.6–8.0 to give indole **1** and, at acidic pH, to give indole-2-carboxylate



28

1 (R^1=R^2=R^3=H)
2 (R^1=R^3=H, R^2=CO_2H)
3 (R^1=Me, R^2=R^3=H)
4b (R^1=R^2=H, R^3=OH)

Scheme 14

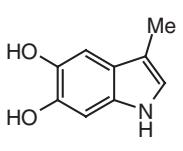
2. Both indoles were obtained as the methyl ethers. The chromophoric and physicochemical properties of 5,6-dimethoxyindole **13** and of 5,6-dimethoxyindole-2-carboxylic acid **23** (R = H) thus obtained were reported. As an extension of Raper's observations, Burton (32JCS546) reported the formation of the *N*-methyl indole **3** by oxidation of 3,4-dihydroxyphenylethylmethylamine with Ag_2O and a simple synthesis of 5,6-dimethoxy-1-methylindole.

In 1937, Green and Richter (37BJ596) reported the conversion of adrenaline to adrenochrome (see Section IVB) which was hydrogenated to give the *N*-methyl indole **3**.

In the early 1950s, Bu'Lock and Harley–Mason (50NAT1036, 51JCS2248) focused their attention on aminochrome rearrangement as a viable route to 5,6-dihydroxyindoles. In all cases, they claimed conversion to the corresponding 5,6-dihydroxyindoles: thus oxidation of dopa and *N*-methyldopa with potassium ferricyanide and $NaHCO_3$ was reported to give indoles **1** and **3**, respectively. The latter was also formed by oxidation of 3,4-dihydroxyphenylethylmethylamine. Other related syntheses of indole **3** were reported by Harley–Mason (50JCS1276) and by Heacock and co-workers (58NAT526) (61CJC231).

Despite the merit of pioneering the biomimetic approach to 5,6-dihydroxyindole synthesis, some of these papers contained incorrect structural conclusions that were highlighted in revisions by subsequent workers. Thus, for example, Heacock and co-workers (63JA1825) provided unambiguous proof that in iodo- and bromo-aminochromes the halogen occupies the 7- and not the 2-position, as previously believed. Independent total syntheses of 5,6-dimethoxy-7-iodoindole and of 5,6-dimethoxy-7-iodo-2-methylindole confirmed this assignment. Another important breakthrough came from a study (85G357) showing that Zn(II) ions induce the non-decarboxylative rearrangement of dopachrome to give the acid **2** rather than the parent indole **1**, as previously reported. The importance of this finding in the chemistry of aminochromes and, by implication, of melanogenesis, is discussed in Section IV. Here it should be noted that for preparative purposes metal ions were recognized as a valuable means for orienting aminochrome **28** rearrangement toward the formation of the acid **2** (Scheme 14).

The syntheses of 2-methyl-5,6-dihydroxyindole **11** (Scheme 2) and 3-methyl-5,6-dihydroxyindole **29** were achieved by Bu'Lock and Harley–Mason (51JCS2248) and by Beer and co-workers (49JCS2061) through cyclization of appropriate 3,4-dihydroxyphenylalanine precursors. A simple preparation of indole **3** was reported by Mattok and Heacock (64CJC484) and involved the oxidation of adrenaline with potassium ferricyanide followed by reduction with ascorbic acid in the presence of ether.



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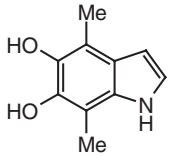


30

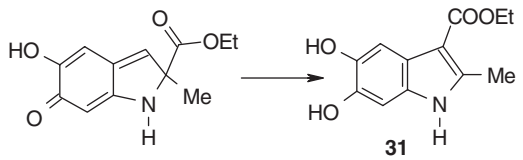
Extension of the synthesis to the 4-methyl (**16**), 7-methyl (**17**) and 4,7-dimethyl (**30**) derivatives was reported by Cromartie and Harley–Mason (53JCS3525) via oxidative cyclization of 3,4-dihydroxy-2- or 5-methylphenylalanine, and by a seven-step approach leading eventually to 2,4,5-trihydroxy-3,6-dimethylphenylethylamine as the ultimate intermediate prior to oxidative cyclization with potassium ferricyanide in $NaHCO_3$.

The potential of 2-substituted-4,5-dihydroxyphenylethylamine derivatives as 5,6-dihydroxyindole precursors was examined by Harley–Mason (53JCS200), who reported a convenient access to 5,6-dihydroxyindole **1** by oxidation of 2-(2,4,5-trihydroxyphenyl)ethylamine with potassium ferricyanide or by autoxidation of 2-(2-amino-4,5-dihydroxyphenyl)ethylamine, the latter obtained in 70% yield by a three-step synthesis. Notably, ferricyanide oxidation proved unsuitable apparently due to the formation of a sparingly soluble complex.

Some years later, Senoh and Witkop (59JA6231) re-examined the oxidation of 2-(2,4,5-trihydroxyphenyl)ethylamine and suggested that the first formed red-coloured species was a cyclised aminochrome intermediate. This conclusion, however, was questioned by Swan (76JCS(P1)339) who reported that the red species produced by oxidation of 2,4,5-trihydroxyphenethylamine was in fact a relatively stable hydroxybenzoquinone derivative which cyclized only slowly to give the aminochrome product and then indole **1**.

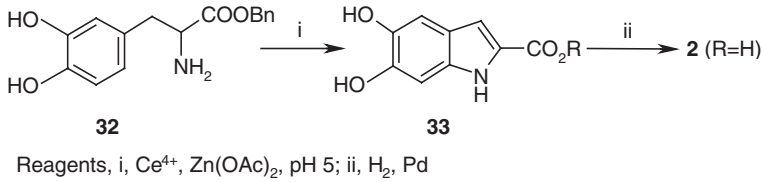
During the 1980s, a number of papers reported straightforward syntheses of 5,6-dihydroxyindole derivatives based on oxidative cyclization of catecholamine compounds. In one study (87TL3775), mushroom tyrosinase was employed in air-equilibrated buffer at pH 6.8 to convert adrenaline, noradrenaline and *N*-isopropylnoradrenaline into 5,6-diacetoxyindole products. In this approach, as in previous ones, the success of the synthesis depended on the efficiency of the cyclization step, which was modest in the case of *N*-isopropylnoradrenaline. Conversion of the resulting aminochrome was achieved by treatment with ascorbic acid in the presence of diethylether followed by immediate acetylation of the organic fraction with acetic anhydride and dimethylaminopyridine.

In another study (82JOC5258), air oxidation of α-methyl-3,4-dihydroxyphenylalanine ethyl ester was shown to lead to ethyl 5,6-dihydroxy-2-methylindole-3-carboxylate **31** via a remarkable 1,2-migration of the ethoxycarbonyl group of the aminochrome intermediate (Eq. (4)). The structure of the product was confirmed by an independent synthesis:

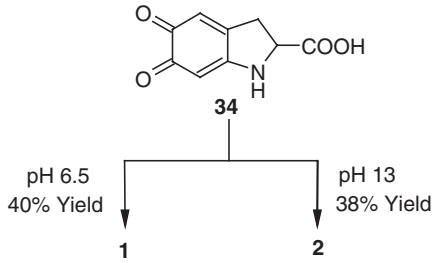


31 (4)

Other workers (87SC1815) reported a convenient one-pot synthesis of the acid **2** and its benzyl ester involving oxidation of dopa benzyl ester **32** with ceric ammonium nitrate followed by treatment with zinc acetate to induce isomerization of dopachrome



Scheme 15



Scheme 16

benzyl ester to the indole benzyl ester **33** (R = Br). Hydrogenolysis of the latter led to the deprotected acid **2** in about 50% overall yield (Scheme 15).

The possibility of orienting the rearrangement of dopachrome **34** through control of pH provided the rationale for a convenient one-pot procedure for indoles **1** or **2** devised by Ito and co-workers (88AB335) (Scheme 16). This reaction is based on the generation of dopachrome by ferricyanide oxidation of dopa at pH 6.5. If the mixture is allowed to stay at the same pH, dopachrome rearrangement proceeds mainly with decarboxylation leading to 5,6-dihydroxyindole **1** (40% yield). However, if the pH is raised to 13 by alkali, under the conditions of absolute exclusion of oxygen, indole-2-carboxylic acid **2** is the main product (38% yield). The role of pH in the isomerization of dopachrome and mechanistic details are discussed in Section IVC. The procedure can be conveniently extended to the synthesis of mono *O*-methylated derivatives of indoles **1** and **2** by treatment with diazomethane and an appropriate use of protection/deprotection steps. Despite the modest yields, and the drawbacks associated with the formation of extensive melanin-like pigments, the procedure remains a viable choice whenever small amounts of material are required.

A short cut entry to indole **3** as the acetyl derivative involving oxidative cyclization of *N*-methyldopamine (epinine) and subsequent acetylation has been reported (93JOC1607).

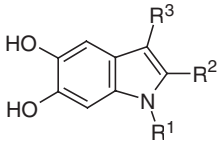
C. Reactions

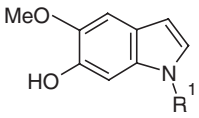
Although the chemistry of 5,6-dihydroxyindoles comprises reactions that are typical of both the indole ring and the catechol moiety, the latter have invariably

overshadowed the former due to the closer relevance to melanin pigmentation, which provided most of the impetus for studies of these indoles. Coverage of the topic, therefore, will necessarily reflect this unbalanced focus on oxidative polymerization.

1. *Oxidation*

a. Semiquinone Formation. Pulse radiolytic one-electron oxidation of 5,6-dihydroxyindole **1** in aqueous solution at pH 7.4, using the azide radical as oxidant, leads to an initial transient spectrum with peaks at 330 and 490 nm with a shoulder at 360 nm (89BBA12). Since a wide variety of *ortho*-semiquinones have peaks around 310 nm, with shoulders around 350 nm, and neutral indolyl radicals have peaks at approximately 320 and 520 nm, it could have been that the initial spectrum corresponded to a mixture of oxygen- and nitrogen-centred radicals. Against this, however, under the conditions chosen, the subsequent decay rates of the peaks at 330 and 490 nm are very similar, and the family of decay spectra exihibit sharp isobestic points, which would not be expected for a mixture of radicals (89BBA12). Studies of: (i) the effect of pH on the initial transient spectrum from 5,6-dihydroxyindole **1** (90JPC6666) (89BBA12); (ii) the corresponding transient absorptions from *N*-methyl-5,6-dihydroxyindole **3** and several methoxylated indoles, in particular 5-methoxy-6-hydroxyindole (**22**) and 5-methoxy-6-hydroxy-*N*-methylindole **35** (90JPC6666) (90BBA319); and (iii) the photooxidation of 5,6-dihydroxyindole monitored by EPR spectroscopy, resulting in the formation of the same semiquinone radical, led to the conclusion that azide radical oxidation of 5,6-dihydroxyindole **1** gives the predominantly oxygen-centred radical, albeit with significant electron delocalization over the nitrogen ring (81PP423), reflected by the visible absorption peak of the radical around 500 nm, typical of the indolic radical.

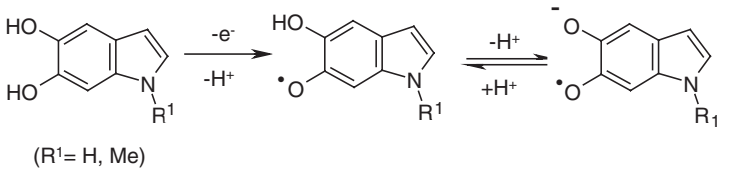




1 (R^1=R^2=R^3=H)
2 (R^1=R^3=H, R^2=CO_2H)
3 (R^1=Me, R^2=R^3=H)
11 (R^1=R^3=H, R^2=Me)
25 (R^1=H, R^2=R^3=Me)
29 (R^1=R^2=H, R^3=Me)

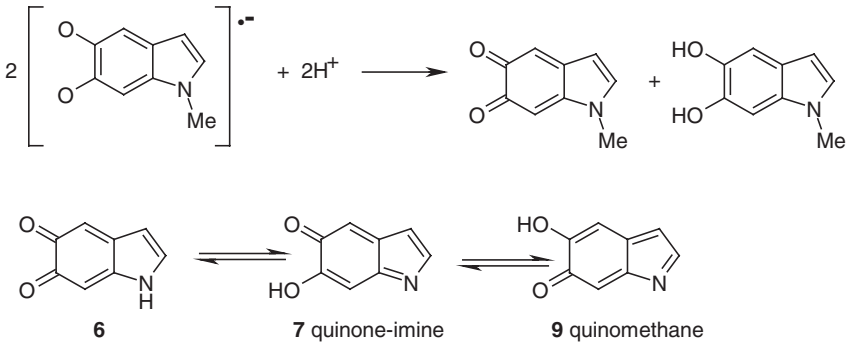
22 (R^1=H)
35 (R^1=Me)

The p*K* values for the hydroxyl groups of the semiquinones derived from both 5,6-dihydroxyindole and *N*-methyl-5,6-dihydroxyindole (Scheme 17) have been reported to be 6.8 (90JPC6666). Similar oxygen-centred semiquinone radicals have been characterized from the one-electron oxidation of the acid **2** (89BBA12), 2- and 3-methyl-5,6-dihydroxyindole (**11** and **29**) and 2,3-dimethyl-5,6-dihydroxyindole **25** (94MR343).



(R1= H, Me)

Scheme 17



6 **7** quinone-imine **9** quinomethane

Scheme 18

The pK values for the semiquinones from 2-methyl- and 2,3-dimethyl-5,6-dihydroxyindole were determined to be 6.6 and 6.3, respectively (94MR343). The rate constants for reaction of azide radicals with all these 5,6-dihydroxyindoles lie in the range 4–8 $\times 10^9\,M^{-1}\,s^{-1}$, i.e. approaching diffusion controlled rates.

Although there is little doubt about the nature of the semiquinones resulting from one-electron oxidation of 5,6-dihydroxyindoles, there is much less certainty regarding the products of decay of these indolesemiquinones. In the case of the semiquinone of 5,6-dihydroxyindole **1**, straightforward disproportionation, a common reaction of many semiquinones (93JCS(F)803) (Scheme 18), results in formation of the corresponding indole-5,6-dione (5,6-indolequinone), but this can exist in tautomeric equilibrium with the corresponding quinomethane **9** and quinone-imine **7** (89BBA12) (see Section V).

Indeed, with pulse radiolysis doses of approximately 20 Gy, the semiquinone of 5,6-dihydroxyindole **1** decays predominantly by second-order kinetics, consistent with disproportionation. The rate constant is dependent upon pH, with values at pH 5.6 and 9.1 being 3.8×10^9 and $1.0 \times 10^8\,M^{-1}\,s^{-1}$, respectively (91JCS(P2)1941). However, with pulse doses of approximately 2 Gy the semiquinone radicals decay predominantly by a first-order process that depends upon the concentration of the 5,6-dihydroxyindole. At pH 8.8, the second-order rate constant for interaction of the semiquinone with the parent was $1.6 \times 10^6\,M^{-1}\,s^{-1}$ (91JCS(P2)1941).

There appear to be at least three separate possible pathways for decay of the semiquinone of 5,6-dihydroxyindole **1**. These are: (i) disproportionation, resulting in the formation of indolequinone **6**, which may rapidly rearrange into the

quinomethane **9** and/or quinone-imine **7**; (ii) reaction with 5,6-dihydroxyindole **1**, leading initially to a dimeric radical anion; (iii) dimerization, via semiquinone coupling.

In the case of pathway (i), it has been argued (91JCS(P2)1941) on the basis of the similarity of the metastable product spectra (with peaks in the 430 nm region) found after the decay of the semiquinones of 5,6-dihydroxyindole **1** and 5-methoxy-6-hydroxyindole **22** (90JPC6666) that the initial product observed after 5,6-dihydroxyindole semiquinone disproportionation is the quinomethane **9**, although a contribution from the quinone-imine **7** was not excluded. For the semiquinone of *N*-methyl-5,6-dihydroxyindole **3**, the initial product of its decay is likely to be solely the *ortho*-quinone (89BBA12). In the case of pathway (iii) stable dimers resulting from the oxidation of 5,6-dihydroxyindoles have been isolated (87T431) (87T4203) (90T5789), although the pulse radiolysis results suggest that these dimers are unlikely to be the main products of semiquinone decay.

Except in the case of the *o*-quinone of *N*-methyl-5,6-dihydroxyindole **3** semiquinone decay, which in turn decays by a single first-order process ($k \sim 10\,s^{-1}$) (90JPC6666) (89BBA12), the subsequent decays of the products arising from 5,6-dihydroxyindole semiquinone decay are complex, involving multiple parent-concentration-independent first-order processes. These may involve nucleophilic reactions, for example, with water or thiols, followed by a variety of condensation steps (89BBA12). *C*(2)- and *C*(3)-Methyl substitution of 5,6-dihydroxyindoles (i.e. **11** and **29**), on the other hand, results in an increased stabilization of the corresponding quinomethanes towards reaction with nucleophiles (94MR343). Under pulse radiolysis conditions, azide itself can react with *o*-quinones (91JCS(F)2939) and quinomethanes (92TL3045) if very high azide concentrations are used.

In order to provide further evidence to distinguish between the various postulated successive post-semiquinone intermediates, it would be useful to apply a more structural technique, such as time-resolved resonance Raman spectroscopy.

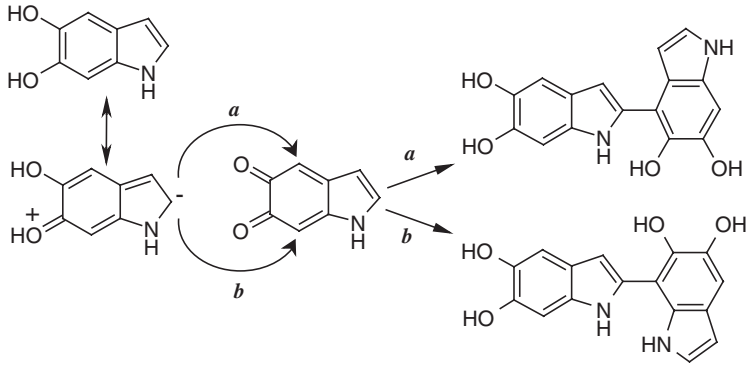
b. Polymerization. Efforts toward the elucidation of the oxidation products of 5,6-dihydroxyindoles are exemplified by the classical studies by Beer and co-workers (54JCS1947) on the autoxidation of several 5,6-dihydroxyindoles, including indoles **1**, **3**, **11**, 5,6-dihydroxy-3-methylindole **29**, 5,6-dihydroxy-2,3-dimethylindole **25**, 5,6-dihydroxy-3-methyl-7-propylindole **26** (R = Me), and 5,6-dihydroxy-2,4,7-trimethylindole. In these studies, measurements of O_2 consumption, spectrophotometric data and elemental analysis were used to conclude that "melanin formation normally involves the 3 (and the 7) position in the polymerization of an intermediate 5,6-quinone."

In spite of pressing reasons for studies of the oxidation of 5,6-dihydroxyindoles, knowledge in this area remained scant and fragmentary for many years, because of the discouraging behaviour of these compounds, which yield on oxidation dark insoluble pigments through complex mixtures of oligomer intermediates. Notably, oligomers of the acid **2** had been found in the *tapetum lucidum* of the catfish (74BJ207). However, their structures were identified only tentatively and not a single species could be isolated and spectroscopically characterized.

A major breakthrough came in 1985 (85TL2805) when the first isolation and structural characterization of a dimer of 5,6-dihydroxyindole **1** paved the way to a series of studies (96G783) which opened up unprecedented vistas into the oxidation chemistry of 5,6-dihydroxyindoles as well as of related carbocyclic monohydroxyindoles, e.g. 4-, 5-, 6- and 7-hydroxyindoles (88T7265) (89T6749). These advances were made possible by an isolation procedure in which the oxidation mixture was reduced with sodium dithionite, extracted with ethyl acetate and acetylated with acetic anhydride/pyridine. Accordingly, most of the oligomers reported in the following discussion are presented as acetyl derivatives. Recently, an improved analytical methodology based on HPLC has allowed isolation of oligomers of the indole **2** in the unprotected form (96T7913).

The structural features of the isolated oligomers show that the mode of polymerization of 5,6-dihydroxyindoles through the 3- and 7-positions proposed in the earlier reports is not correct. In particular, the modes of coupling of the parent indole **1** and related 5,6-dihydroxyindoles show an unanticipated propensity to couple through 2,2′-, 2,4′- and 2,7′-linkages, as highlighted by the structures of the main dimers isolated from oxidation of indoles **1**, **3** and their derivatives. Such a mode of coupling stems from the particular dioxygenation pattern pertaining to the 5,6-dihydroxyindole system, which directs significant electron density onto the 2-position of the indole ring. In any case, the course of oxidation depends on the nature of the oxidant, the pH of the medium and the presence of substituents. Thus, the electron-withdrawing carboxylate group in the acid **2** diverts reactivity from the pyrrole moiety of the indole ring to a significant extent, whereby coupling occurs preferably through the 4- and 7-positions, with only minor involvement of the 3-position. Although the precise mechanism of oxidative coupling of 5,6-dihydroxyindoles remains elusive, product analysis suggests that the process involves nucleophilic attack of the indole system onto an oxidized electrophilic counterpart, possibly the 5,6-indolequinone intermediates generated in the process (Scheme 19).

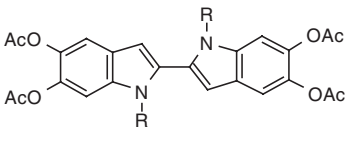
A more detailed discussion of the evidence supporting the involvement of 5,6-indolequinones in 5,6-dihydroxyindole oxidation will be presented in Section V. The following discussion will be limited to listing the main oligomeric products



Scheme 19

isolated from the oxidation of the various 5,6-dihydroxyindoles, passing over the many mechanistic implications and the relevance to melanin structure, for which the interested reader is referred to reviews and book chapters (96G783, 95MI94, 98MI307).

Upon enzymatic oxidation, chemical oxidation or autoxidation, indoles **1** and **3** afford in the early stages mixtures of dimers and trimers (85TL2805) (86T2083) (90T5789) (91BBA423). These include the symmetric 2,2′-bindolyls **36** (R = H, Me), which are formed only by autoxidation in the presence of transition metal ions, and the asymmetric 2,4′- and 2,7′-biindolyls **37** (R = H, Me) and **38**. Isolated trimers included the terindolyls **39** (R = H, Me), **40**–**41**.



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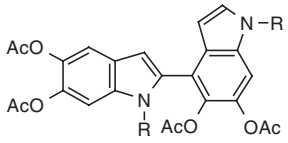

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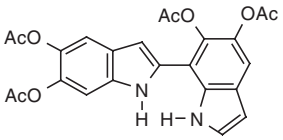

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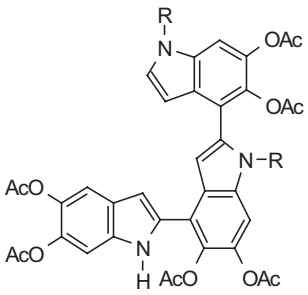

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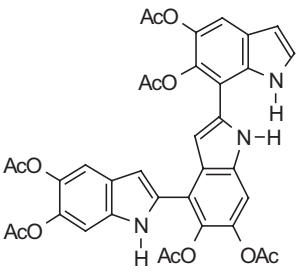

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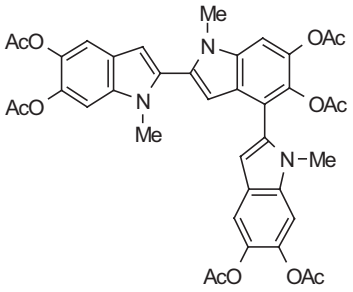
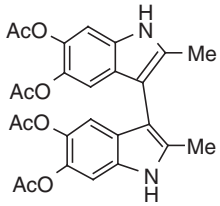


41

Oxidation of 5,6-dihydroxy-2-methylindole **11** with peroxidase/H_2O_2 gave mainly 3,3′-biindolyl **42**, 7,7′-biindolyl **43**, 3,4′-biindolyl **44**, 3,7′-biindolyl **45**, and the bridged dimer **46**, as well as one terindolyl **47**, another trimer with a methylene bridge **48** and the remarkable trimer **49** featuring a tetrahydrocyclopentadiindole ring system (93T9143). Oxidation of 5,6-dihydroxy-2,3-dimethylindole **25** gave mainly the corresponding indolequinone (96TL4241) (see Section V).



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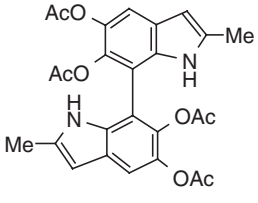

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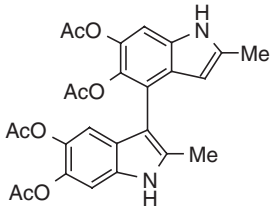

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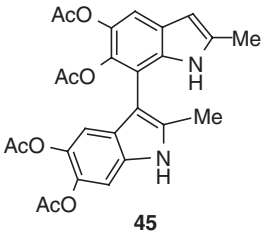

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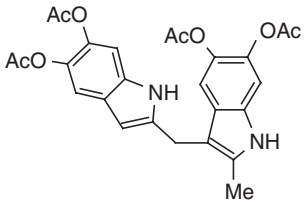

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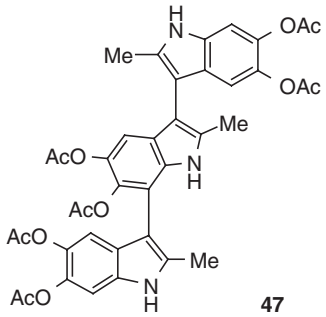

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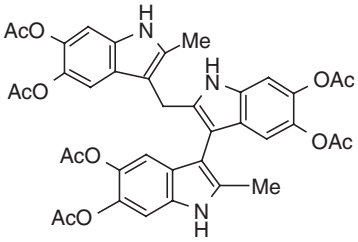

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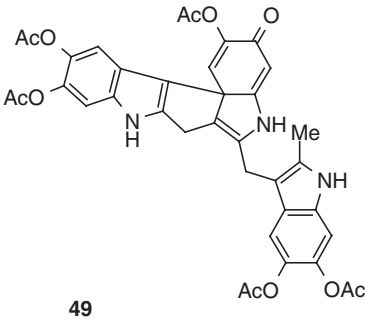
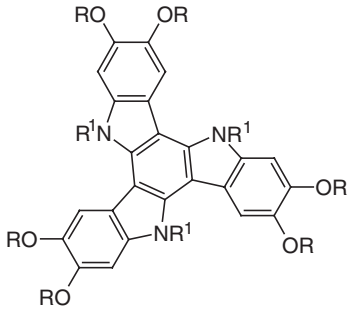


49

Although the *o*-dihydroxy moiety dictates the reactivity of 5,6-dihydroxyindoles toward oxidising agents, in acidic medium or in the *O*-protected derivatives, the normal oxidative coupling routes are precluded and alternative reaction channels become operative. Thus oxidation of 5,6-dihydroxyindole **1** in acidic aqueous media leads to isomeric hexahydroxydiindolocarbazoles, isolated as the acetyl derivatives **50a** (29%) and **51a** (19%) (98JOC7002). Similar oxidation of the *N*-methyl- (**3**) and *O,O*-dimethyl- (**13**) derivatives affords the corresponding diindolocarbazoles **50b**,**c** and **51b**,**c** in up to 70% overall yield, whereas 5,6-diacetoxyindole **12** failed to give cyclotrimerization products.



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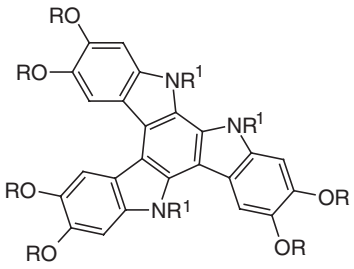


51

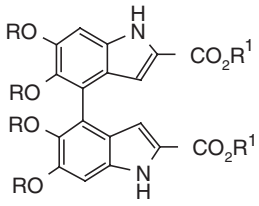
a, R = $COCH_3$, R^1 = H

b, R = $COCH_3$, R^1 = CH_3

c, R = CH_3, R^1 = H

Formation of diindolocarbazoles could be explained by a mechanism in which the electron-donating substituents favour an array of acid-induced couplings and subsequent dehydrogenation steps driven by the energetically favourable closure of the fused aromatic framework.

Oxidation of the acid **2** leads mainly to the 4,4′-biindolyl **52**, the 4,7′-biindolyl **53** and the terindolyl derivative **54** (87TL467) (87T4203). In subsequent studies, a more complex mode of polymerization of indole **2** was disclosed, involving formation, besides the 4,4′ and 4,7′ coupled dimers, of three new dimers, the 3,4′-, 3,7′- and 7,7′-biindolyls **55**, **56** and **57** ($R = R^1 = H$), respectively, which could be isolated without derivatization (96T7913).



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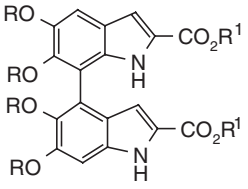
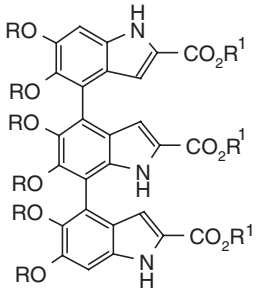


53

a: R = $COCH_3$, R^1= CH_3
b: R=R^1=H



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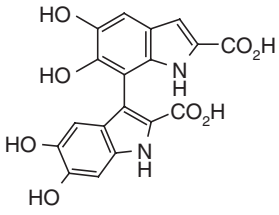

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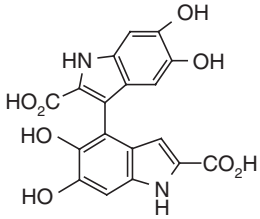
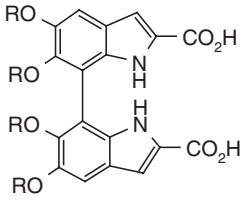


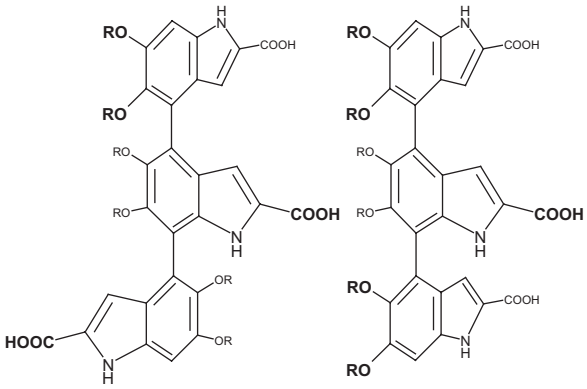
56



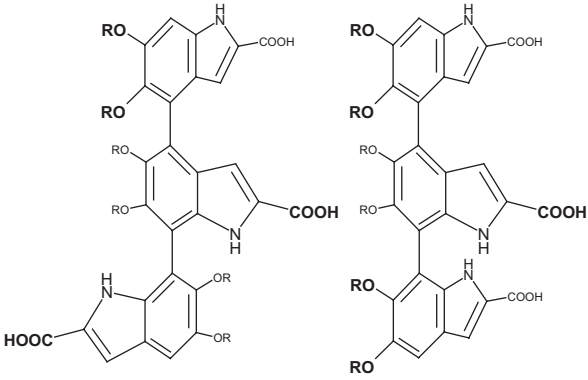
57

In a more recent reexamination of this topic (02T3681) **54** ($R = COCH_3$, $R^1 = H$) and three new linear trimers (**58**–**60**, $R = COCH_3$) in eight atropoisomeric forms were isolated and characterized, giving the first evidence for the chiral nature of these early oligomeric species.

A subsequent investigation of chirality in such systems allowed the isolation of the regiosymmetric tetramer **61** by means of a model approach involving oxidation of the main dimer, i.e. the 4,4′-biindolyl **52b** (03TA1133). The resolution of the enantiomers of **52**, **53**, **57** ($R = COCH_3$) and all the diasteroisomers of **61** ($R = COCH_3$, $R' = H$) was achieved and their absolute stereochemistry was deduced by the exciton chirality method.



54



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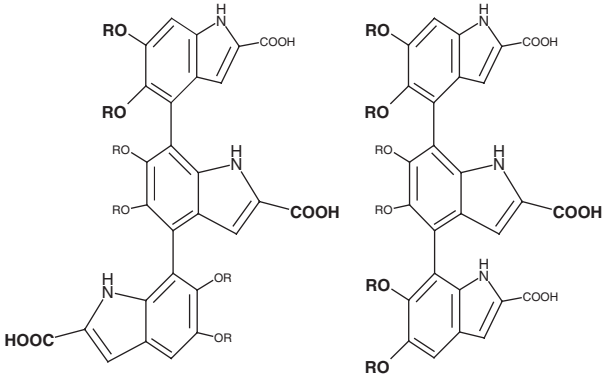
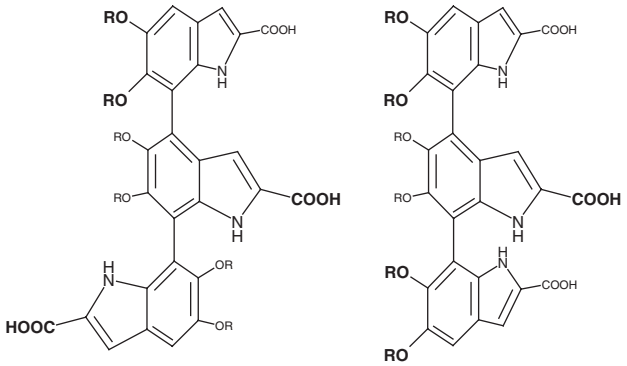
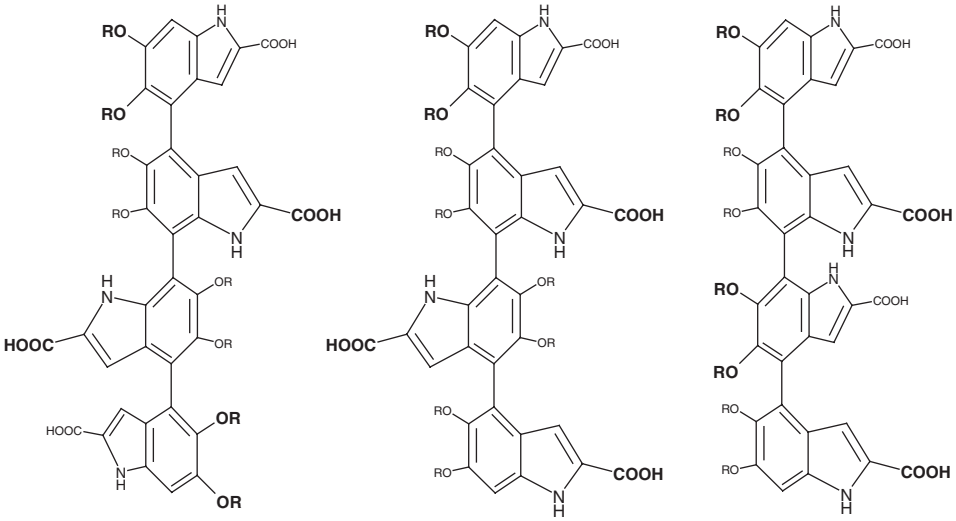


59



60

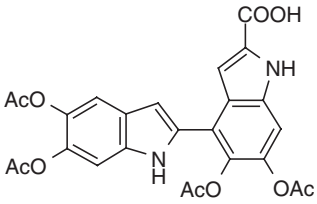
(Only one enantiomer is represented for each atropoisomer. Diastereoisomers are indicated with the same numbering)



61

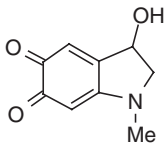
Only one enantiomer is represented for each atropoisomer

Mixed-type oligomers of the type **62** can be formed when indoles **1** and **2** are co-oxidized with peroxidase/hydrogen peroxide (93TL885), suggesting that these indoles may co-polymerize *in vitro* to some extent.

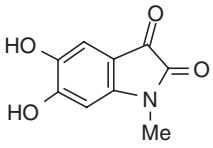


62

Under aerobic conditions, oxidation of adrenochrome **63** leads to the formation of 5,6-dihydroxy-1-methyl-2,3-indoledione **64** and the corresponding 4,4′-biindolyl **65**, which conceivably arise via rearrangement to adrenolutin **4** and subsequent oxidation (88T6441).



63



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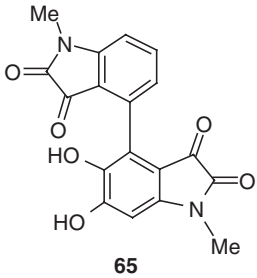
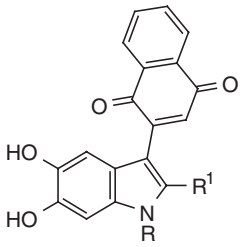


65

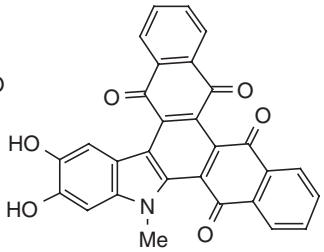
Other studies in the field concern the oxidation of 5,6-dihydroxytryptamine in relation to the mechanism of neurotoxicity in the central nervous system. In aqueous solution at pH 7.2, the neurotoxin is converted to 2,7′-*bis*(5,6-dihydroxytryptamine) (90JMC3035). A minor route involves the formation of two trihydroxytryptamines and other products.

2. *Reactions with Electrophiles*

Studies of the reactions of 5,6-dihydroxyindoles with electrophiles are rare. The main problem is the marked tendency of the system to undergo oxidation rather than substitution or addition. This dual behaviour is exemplified by the reaction of 5,6-dihydroxyindole **1** and its 1-methyl (**3**) and 2-methyl (**11**) derivatives with quinones (87T2749). Whereas 1,4-naphthoquinone gives deep-violet monoadducts **66a**–**c** and a dinaphthocarbazole **67**, *para*-benzoquinone gives mainly oligomeric oxidation products and melanin-type material.



66



67

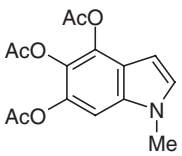
a: R = R^1= H
b: R= Me, R^1= H
c: R= H, R^1 = Me

5,6-Dihydroxyindoles have also been reported to react with α-diketones: thus the reaction of indole **3** with dehydroascorbic acid (64CJC1401) leads to the formation of a 1,4-dibenzodioxane derivative.

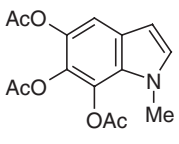
3. *Photochemistry*

The photochemical behaviour of 5,6-dihydroxyindoles has attracted continuing interest because of the possible relevance to the mechanisms of skin photoprotection and UV-induced persistent sun tanning. Koch and Chedekel (87PP229) showed that continuous-wave photolysis of indoles **1** and **2**, or their 5-*O*-methylated metabolite, with UV radiation of wavelengths >300 nm resulted in rapid destruction of starting material. Using electron spin resonance (ESR) spin-trapping techniques, initial production of free radical species was observed and prolonged photolysis resulted in the formation of polymeric photoproducts. Radicals were trapped by the nitrone spin trap DMPO and characterized by their ESR spectra as hydrated electrons and H atoms. While the parent indole **1** photoionizes, the acid **2** does not ionize appreciably upon irradiation, but rather undergoes hydrolysis of X–H bonds.

Photooxidation of indole **3** in methanol with Pyrex-filtered UV light gave a complex mixture of products which could be isolated and identified after acetylation as the 2,4′-biindolyl **37** (R = Me), two triacetoxyindoles (**68**, **69**), 5,6-diacetoxy-1-methyloxindole (**70**) and two pentaacetoxybiindolyls (**71**, **72**) (87T431). This product pattern was clearly different from that obtained by chemical or enzymatic oxidation, suggesting the involvement of excited states of the indole and their interaction with oxygen.



68



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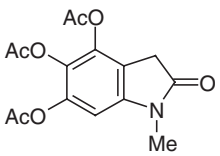

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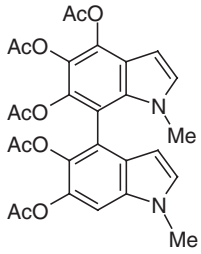
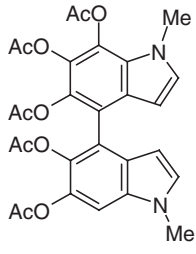
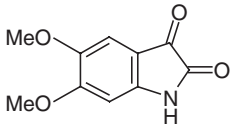


71

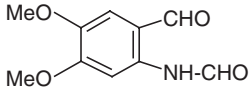


72

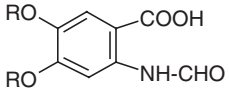
Similar photooxidation of indole **13** in methanol gave the isatin **73** and 2-formamido-4,5-dimethoxybenzaldehyde **74** (86G407). The formation of an oxygenation product by direct photooxidation was specifically characteristic of 5,6-dialkoxyindoles since 5,6-diacetoxyindole **12** gave no isolable product. Conversely, using acetone as the solvent, the reaction gave *N*-formylanthranilic acid derivatives in good yield. Thus indole **13** gave 2-formamido-4,5-dimethoxybenzoic acid **75a** in 40% yield and indole **12** gave 2-formamido-4,5-diacetoxybenzoic acid **75b** in 50% yield. The effect of acetone on the reaction course can be ascribed to the involvement of the excited triplet state of the ketone. This may induce H-atom abstraction from a peroxide intermediate leading to a radical species that is eventually converted to the ring-opened carboxylic acid derivative following coupling with oxygen:



73



74



75 **a**, R = CH_3
b, R=$COCH_3$

III. 2,3-Dihydro-5,6-dihydroxyindoles (5,6-Dihydroxyindolines)

A. Physical Properties

1. *Ultraviolet Spectroscopy*

The UV spectra of several derivatives **76** and **77** have been recorded and these are summarized in Table 4.

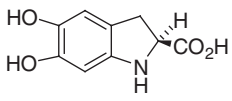
2. *NMR Spectroscopy*

Several studies have reported the chemical shifts of the ring protons in 5,6-dihydroxyindoline derivatives and these are tabulated in Table 5.

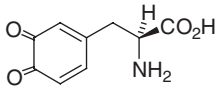
Table 4. Ultraviolet spectral data for 5,6-dihydroxyindoline derivatives

Structure	R^1	R^2	R^3	R^4	Solvent	λ_{max} (ε) (nm)	References
76	Ac	CO_2Me	H	H	MeOH	306 (8050), 258 (10900), 214 (26200)	68HCA1476
76	Ac	CO_2Me	Ac	Ac	MeOH	288 (4900), 250 (14500), 210 (17200)	68HCA1476
					EtOH	292sh, 288, 250, 207	70HCA1704
					EtOH	292 (5500), 288 (5370), 253 (15500)	68NKZ760
76	CO_2Bn	CO_2H	H	H	EtOH	304, 245, 207	70HCA1704
76	Ac	CO_2H	Ac	Ac	EtOH	289, 251, 207	70HCA1704
76	H	CO_2Me	Ac	Ac	EtOH	302, 248, 204	70HCA1704
76	H	CO_2H	Glu	H	H_2O (pH 11)	311 (5000)	84HCA1348
76	CHO	CO_2H	Glu	H	H_2O	307 (10500), 253 (11100)	84HCA1348
77	H	CO_2H	H	H	20%HCl	285 (4150), 210 (9230)	68HCA1476
77	H	CO_2Me	H	H	1 N HCl–MeOH	291 (4200)	68HCA1476
77	H	CO_2Me	Ac	Ac	EtOH	304 (3810), 244 (6840)	77JOC4153
77	H	CO_2H	Glu	H	H_2O (pH 3)	284 (3400)	84HCA1348
77	Me	H	H	H	H_2O (pH 7.4)	310sh (1500), 290 (3360)	00JCS(P1)4306
77	nPr	H	H	H	H_2O (pH 7.4)	312sh (1450), 290 (4120)	00JCS(P1)4306
77	nPr	H	Me	Me	H_2O (pH 7.4)	284 (4115)	00JCS(P1)4306

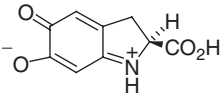
B. PREPARATION



78 L-cyclodopa (leucodopachrome)



79 dopaquinone



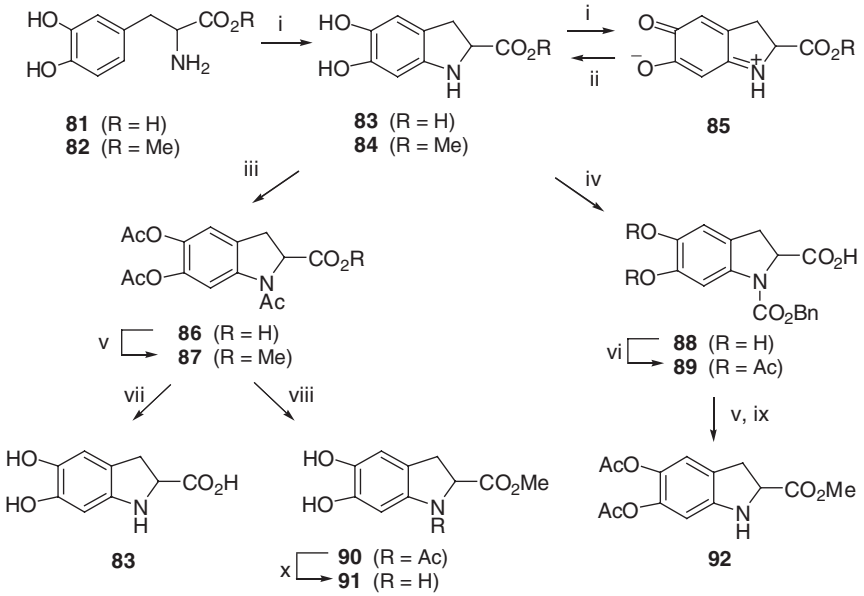
80 dopachrome

The most significant 2,3-dihydro-5,6-dihydroxyindole is L-cyclodopa **78**, also known as leucodopachrome, which is an intermediate in the biosynthesis of eumelanin and is formed by the spontaneous cyclization of dopaquinone **79** (92MI2) (04MI1). In turn, cyclodopa is readily oxidized to dopachrome **80** but this oxidation can be reversed chemically using sodium dithionite. Wyler and Chiovini have described the preparation of both enantiomers of cyclodopa using transformations

Table 5. Chemical shifts of ring protons in 5,6-dihydroxyindoline derivatives

Structure	R^1	R^2	R^3	R^4	Solvent	δH-2	δH-3	δH-4	δH-7	References
76	CO_2Bn	CO_2H	H	H	d_6-DMSO	4.85	3.4,2.9	6.6	7.4	70HCA1704
76	H	CO_2Me	Ac	Ac	$CDCl_3$	4.43	3.31	6.55	6.95	77JOC4153
					$CDCl_3$	4.43	3.33	6.49	6.88	70HCA1704
76	Ac	CO_2Me	Ac	Ac	d_6-DMSO	5.25	3.2,3.6	7.04	7.71	70HCA1704
					$CDCl_3$	4.95	3.3,3.5	6.98	8.05	68NKZ760
76	Ac	CO_2H	Ac	Ac	d_6-DMSO	5.20	3.2,3.6	7.19	7.88	70HCA1704
76	H	CO_2H	Glu	H	D_2O	4.68	3.3,3.5	6.99	7.19	84HCA1348
76	CHO(*E*)	CO_2H	Glu	H	D_2O	4.91	3.1,3.5	7.06	6.86	84HCA1348
76	CHO(*Z*)	CO_2H	Glu	H	D_2O	4.99	3.2,3.5	7.06	7.50	84HCA1348
76	H	H	Me	Me	$CDCl_3$	~3.5	2.8–3.2	6.39	6.81	78JMC548
Betanidin	See **120**	CO_2H	H	H	TFA	5.56	3.3–4.1	7.15	7.4	84HCA1793
77	H	H	H	H	d_6-DMSO	3.72	3.08	6.88	6.84	95JMC917
					D_2O	3.67	3.03	6.90	6.86	78JMC548
77	H	CO_2H	H	H	TFA	5.36	3.6,3.9	7.05	7.34	68HCA1476
77	H	CO_2Me	Ac	Ac	d_6-DMSO	4.66	3.27	6.69	7.03	77JOC4153
77	H	CO_2H	Glu	H	TFA	5.34	3.6,3.9	7.29	7.34	84HCA1348
77	Me	H	H	H	D_2O	3.85	2.98	6.51	6.64	00JCS(P1)4306
77	Me	H	Me	Me	D_2O	4.09	3.24	6.99	7.16	00JCS(P1)4306
77	NPr	H	H	H	D_2O	3.99	3.07	6.63	6.67	00JCS(P1)4306
77	NPr	H	Me	Me	D_2O	4.23	3.19	6.70	7.61	00JCS(P1)4306

shown in Scheme 20 (68HCA1476). Oxidation of L-(or D-) dopa methyl ester **82** by potassium ferricyanide at pH 8 gives L-(or D-) dopachrome methyl ester **85** (R = Me) via cyclization of the intermediate *ortho*-quinone and further oxidation. Using sodium dithionite the dopachrome ester **85** (R = Me) is reduced back to the cyclodopa methyl ester **84**, which is not isolated but converted to the crystalline *O,O,N*-triacetyl derivative **87**. Cyclodopa **78** is obtained by the treatment of ester **87** with aqueous HCl at 80 °C under vacuum. This method was used to prepare L-cyclodopa for recent pulse radiolysis studies of eumelanogenesis (03PCR487). Using methanolic HCl the triacetyl derivative **87** can be converted to the *N*-acetyl ester **90** or to the unsubstituted ester **91** (68HCA1476). The preparation of the ester **90** has also been reported by a Japanese group (68NKZ760). Commencing with ferricyanide oxidation of L-dopa **81**, Wölcke and co-workers have prepared both the *O,O,N*-triacetyl acid **86** and methyl ester **87**, and also the *O,O*-diacetyl ester **92** and the *N*-benzyloxycarbonyl acids **88** and **89** (70HCA1704).

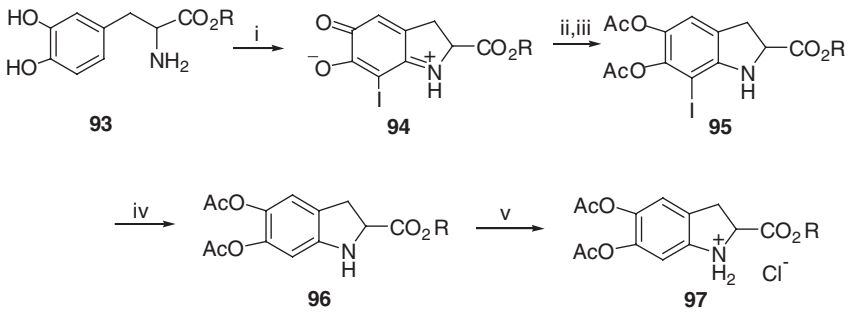


Reagents: i, $K_3[Fe(CN)_6]$; ii, $Na_2S_2O_4$; iii, Ac_2O/pyridine; iv, $BnO_2C.Cl$; v, CH_2N_2; vi, Ac_2O; vii, HCl/H_2O at 80 °C; viii, NH_4OH/MeOH or HCl/MeOH at 40 °C; ix, Pd/H_2; x, HCl/MeOH at 80 °C.

Scheme 20

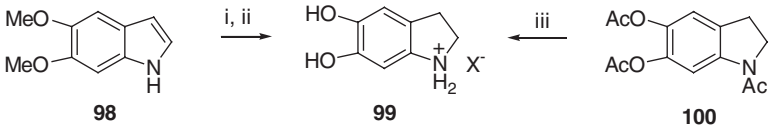
Büchi and Kamikawa reinvestigated the earlier work of Bu'Lock and Harley–Mason and showed that potassium iodate oxidation of racemic dopa esters **93** (R = Me, Et) followed by dithionite reduction and acetylation gives the 5,6-diacetoxy-7-iodo esters **95** (R = Me, Et) (Scheme 21) (77JOC4153) (51JCS2248). Catalytic reduction removes the 7-iodo substituent and the esters **96** can then be hydrolysed to cyclodopa using known methods (Scheme 20). The 2,3-dihydroindoles **96** were fully characterized by conversion to the salts **97**. The intermediate aminochrome **94** (R = Me) was isolated and characterized. See Section IVB for further details on the mechanism of iodination during this oxidation.

Formation of cyclodopa derivatives by catalytic reduction of appropriate indole-2-carboxylic acids failed to give the desired indolines although chemical reduction of 5,6-dimethoxyindole-2-carboxamide gave a crude product presumed to be cyclodopa (70JCS(C)865). However, sodium cyanoborohydride reduction of 5,6-dimethoxyindole **98** gives the 2,3-dihydroindole in good yield and treatment with 48% HBr affords the parent 2,3-dihydro-5,6-hydroxyindole as its hydrobromide salt **99** (X = Br) (78JMC548) (95JMC917). In an alternative procedure the chloride **99** (X = Cl) has been obtained by oxidative cyclization of dopamine (cf. Scheme 20) leading to the triacetyl derivative **100** followed by the treatment with hydrochloric acid (Scheme 22) (70G693).



Reagents: i, KIO_3; ii, $Na_2S_2O_4$; iii, Ac_2O/pyridine; iv, Pd/H_2; v, dry HCl.

Scheme 21

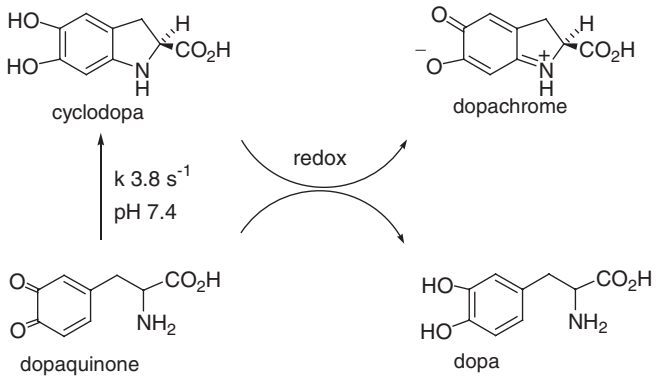


Reagents: i, $NaBH_3CN$; ii, HBr; iii, HCl.

Scheme 22

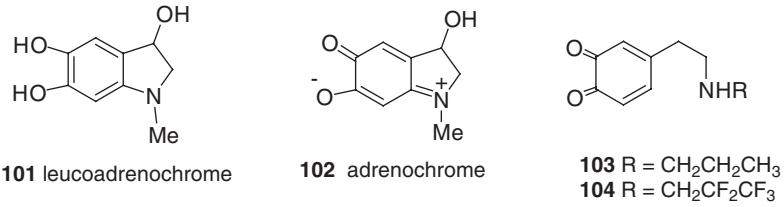
Other primary catechol amines have been cyclized to the corresponding 2,3-dihydroindole by oxidation to the *o*-quinone. These include dopamine (83JOC562) (94JMC1084) (95JCS(P2)259) (97JCS(D)2813) (02AC5047), α-methyldopamine (83JOC562), α-methyldopa (80JOC2899), *β*,*β*-dimethyldopamine (01JA9606), noradrenaline (98JCS(D)1315), and α-methylnoradrenaline (83JOC562) although the products have not necessarily been isolated due to facile further oxidation. In many of these studies emphasis has been on the kinetics of the process rather than preparative methods. Because of the biosynthetic relevance to melanin formation, the kinetics of the cyclization of dopaquinone **79** to cyclodopa **78** in aqueous media has received particular attention (74JOC1980) (01JPP(B)123). Pulse radiolysis studies have shown that at pH 7.4 dopaquinone rapidly decays with first-order kinetics ($k = 3.8\,s^{-1}$) to give dopachrome **80** (03PCR487). The rate-determining step is cyclization to cyclodopa which, as soon as it is formed, is further oxidized by uncyclized dopaquinone to give dopachrome and dopa (Scheme 23). The cyclization is strongly catalysed based. The rapid redox exchange between cyclodopa and dopaquinone to form dopa is relevant to the kinetics of tyrosinase oxidation of tyrosine (03ACR300).

Secondary catechol amines upon oxidation also cyclize to the 2,3-dihydroindoles which rapidly undergo further oxidation to the aminochrome. Typically, adrenaline gives adrenochrome **102** via leucoadrenochrome **101**. Few examples of the intermediate indolines (e.g. **101**) have been fully characterized. Work in this area



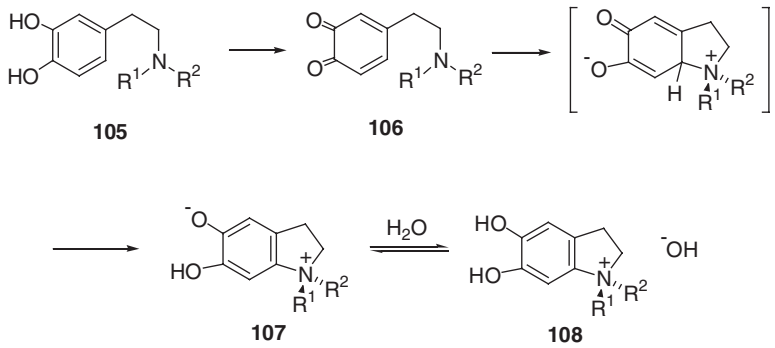
Scheme 23

up to 1965 has previously been reviewed (65AHC205) and little new work has appeared (68B3089) (91PHA426) (93PHA273) (93JCS(P2)2435). Powell and Heacock have provided spectroscopic evidence that at pH 3–4 aminochromes (e.g. **102**) react with thiols to give 4-thiosubstituted-5,6-dihydroxyindolines (74CJC1019).



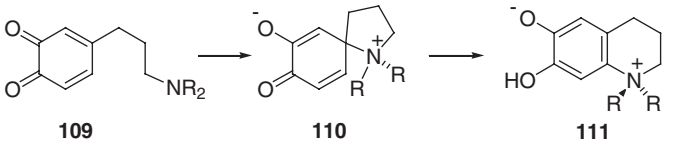
A pulse radiolysis study of the cyclization of the secondary amine **103** showed that the rate is at least an order of magnitude faster than that for dopa or dopamine under similar conditions (03PCR397). This was attributed to the secondary amine being a better nucleophile. The rate of cyclization of the pentafluoro derivative **104** is an order of magnitude slower than that of the unfluorinated quinone **103**, presumably due to the electron-withdrawing power of the substituent. Others, using cyclic voltammetry, have also observed an increase in cyclization rate of quinone amines in changing from primary to secondary amines. The cyclization rate of adrenaline is 140 times faster than noradrenaline (67JA447). Castagnoli and co-workers have also shown that an *N*-methyl substituent dramatically increases cyclization rate (78JMC548). Since no correlation was observed with calculated pK_a values, they concluded that the difference is due to inherent differences in nucleophilicity (78JMC548). Cyclization rates for tertiary amines such as *N*,*N*-dimethyl are even faster (see below).

The oxidation of tertiary catechol amines **105** is of particular interest since the products **107** contain a quaternary nitrogen and cannot undergo further oxidation to an aminochrome (Scheme 24). In a recent study, several examples of the betaines **107**



Scheme 24

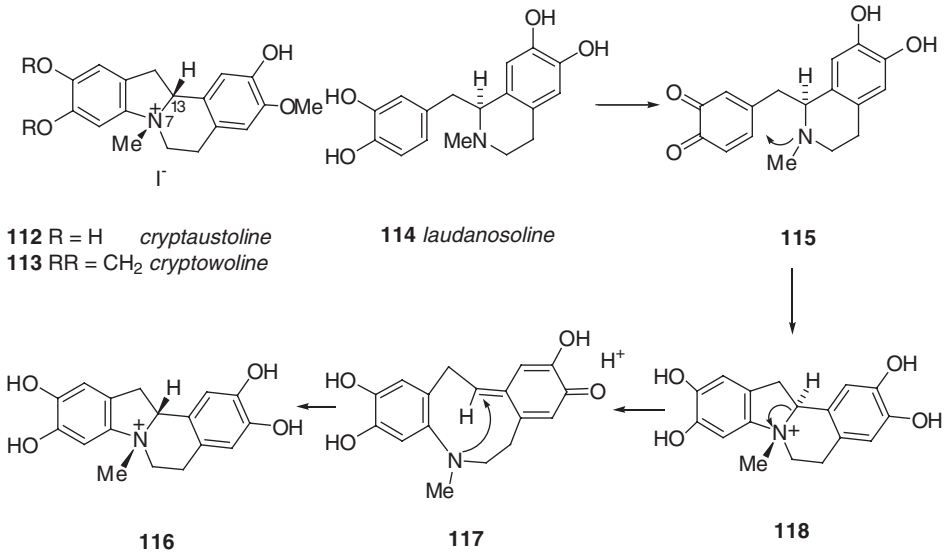
have been prepared, by oxidation of the catechol using dianisyltellurium oxide, and characterised (98JCS(CC)77) (00JCS(P1)4306). Under aprotic conditions, such as organic solvents, the products are betaines **107** but in aqueous acidic conditions salt formation **108** occurs. These synthetic products have been shown to be identical to the products of tyrosinase oxidation of the tertiary amines **105**, and the corresponding phenol amines, and these studies have shed light on the mechanisms of tyrosinase oxidation of tyramine and dopamine derivatives (97JBC26226). The cyclizations **106**→**107** (R = Me, nPr) in aqueous media have been studied by pulse radiolysis and the observed/apparent first-order rate constants found to be $300\,s^{-1}$(R = Me) (pH 6.2) (00JCS(P1)4306) and $48\,s^{-1}$ (R = nPr) (pH 6.0) (97JBC26226), which are faster than dopaquinone **79** ($0.9\,s^{-1}$ at pH 6.6) (84JCS(CC)1170) and the secondary amine **103** ($<27.2\,s^{-1}$ at pH 6.0) (03PCR397). It is interesting to note that a study of the higher homologues **109** showed that the initial product is the kinetically favoured 5-*exo-trig* spiro betaine **110**, which then gives the thermodynamic product **111** (00JCS(P1)4306).



The cyclization of tertiary amine derivatives of *ortho*-quinones was first encountered independently by Robinson (32JCS789) and by Schöpf (32LA22), who showed that oxidative cyclization of racemic laudanosoline **114** gave a tetracyclic 2,3-dihydroindole derivative (e.g. **118**), presumably via the *ortho*-quinone **115**. On the basis of this observation, Robinson suggested that derivatives of these oxidation products of laudanosoline might one day be found in nature. Subsequently, the natural products (−)-cryptaustoline **112** and cryptowoline **113** were isolated (52NAT618) and synthesized (92JA8483 and papers cited therein). Meyers and co-workers have reported an asymmetric synthesis of (+)-cryptaustoline

and on the basis of its properties have revised the assignment of the absolute configuration of the natural product (−)-cryptaustoline **112** which is now recognized as having the (13*R*,7*S*) configuration **112** (91JA2789) (92JA8483). The origin of the original misassignment of the absolute configuration of (−)-cryptaustoline is interesting and arose from the assumption that preparation (67AGE799) from (+)-laudanosoline **114** occurred with retention of configuration (73CPB1839) at C-13 (Scheme 25). In an elegant study, the Colorado group (92JA8483) have shown that oxidative cyclization of (+)-laudanosoline **114** is kinetically controlled giving the *trans*-product **118** but that this initial product, due to significant strain, rearranges to the *cis*-product **116** via the ring-opened *p*-quinomethane **117**.

Other naturally occurring 5,6-dihydroxy-2,3-dihydroindole derivatives are *betanin* **119**, which is the red-violet pigment of beet, and the aglycone *betanidin* **120** (62HCA638). These structures contain the 1,7-diazaheptamethinium chromophore and inspection of the resonance forms **119A** and **119B** clearly reveals their structural relationship to L-cyclodopa **78**. *Betanidin* **120** has been prepared as a 4:6 mixture of epimers (2*S*,15*S* (natural) and 2*S*,15*R*) by condensation of the semicarbazone **121** with the methyl ester of L-cyclodopa followed by saponification of the triester (84HCA1547). The same group have synthesized a number of *betanidine* analogues some of which retain a 2,3-dihydro-5,6-dihydroxyindole fragment (62HCA640) (85HCA1670) (86HCA1588). In solution *betanidine* is a mixture of interconverting (12*E*)- and (12*Z*)-stereoisomers (84HCA1793). *Betanidin* has been formed *in vitro* from dopa **81** by a combination of enzymatic and spontaneous transformations by consecutive incubation with *dopa dioxygenase* (from *amanita muscaria*) and *tyrosinase* (from *portulaca grandiflora*) (98P1593) (98CNC512).



112 R = H *cryptaustoline*
113 RR = CH_2 *cryptowoline*

114 *laudanosoline*

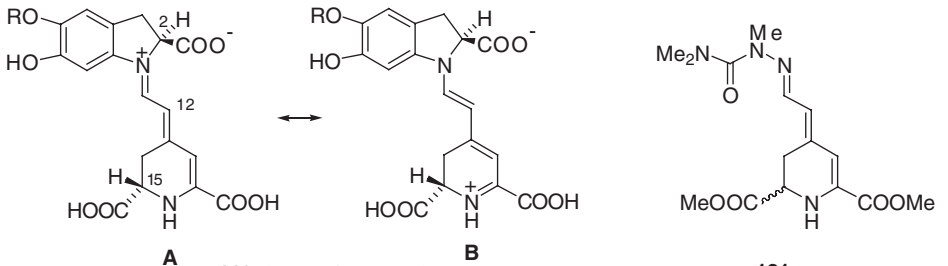
115

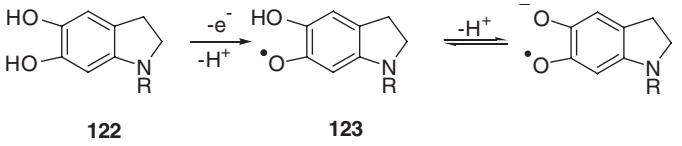
116

117

118

Scheme 25



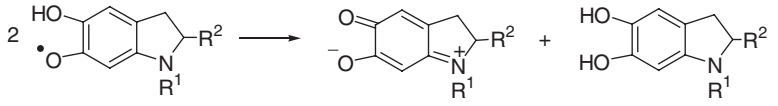


Scheme 26

C. Reactions

1. *Oxidation*

a. Semiquinone Formation. Pulse radiolytic one-electron oxidation of the 2,3-dihydro-5,6-dihydroxyindoles **122** (R = H, Et) results in the formation of the corresponding semiquinones **123** (96JCS(P2)241), with spectra rather similar to those of the radicals derived from the dihydroxyindoles (see Section IIC1a). The p*K* value for 2,3-dihydro-5,6-dihydroxyindole semiquinone **123** (R = H) (Scheme 26) was determined to be 5.3 (96JCS(P2)241). At pH 7.4, the closely related semiquinone of cyclodopa **78**, formed by one-electron oxidation by the dibromide radical anion ($k = 6.9 \times 10^8\ M^{-1}\ s^{-1}$), has a similar absorption profile to the acid form of 2,3-dihydro-5,6-dihydroxyindole semiquinone **123** (R = H), implying that the p*K* of the cyclodopa semiquinone is considerably higher (03PCR487).

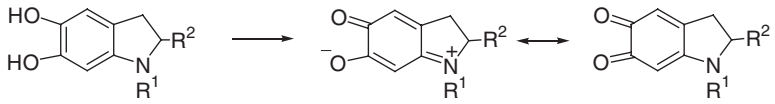


124 **125** **126** (5)

The semiquinones of the 2,3-dihydro-5,6-dihydroxyindoles **124** (R^1 = H, Et, R^2 = H), generated by pulse radiolysis, were found to decay via simple bimolecular disproportionation to the aminochromes **125** (R^1 = H, Et, R^2 = H) and the corresponding 2,3-dihydroindoles **126** (Eq. (5)) (96JCS(P2)241). Consistent with this interpretation, the corresponding semiquinone from cyclodopa **124** (R^1 = H, $R^2 = CO_2^-$) disproportionates into dopachrome **125** (R^1 = H, $R^2 = CO_2^-$) and

cyclodopa **126** ($R^1 = H$, $R^2 = CO_2^-$) (03PCR487). Some paramagnetic metal ions, such as Zn^{2+}, can interact with catecholic semiquinones (85EHP185), modifying their reactions, and this applies to the semiquinones of 2,3-dihydro-5,6-dihydroxyindole **123** (R = H) (96JCS(P2)241) (and 5,6-dihydroxyindole (81PP423)), the former semiquinone complexing with Zn^{2+} with a rate constant of $3 \times 10^6\,M^{-1}\,s^{-1}$ at pH 5.0 (96JCS(P2)241).

b. Aminochrome Formation. 5,6-Dihydroxyindolines are readily oxidized to the corresponding *ortho*-quinones (Eq. (6)), which are generally known as aminochromes (65AHC205) and are usually represented by the dipolar resonances structures **127A** rather than as the quinone **127B**. The preparative oxidation of 5,6-dihydroxyindolines to aminochromes is discussed in Section IVB. A wide variety of oxidizing agents achieve this transformation. One-electron oxidation results in the formation of the semiquinone which disproportionates leading to the aminochrome (Eq. (5)) (Section IIIC1a).

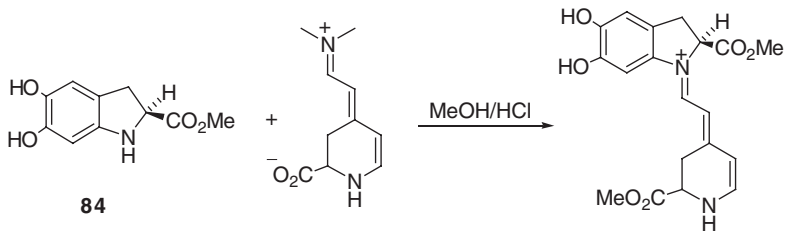


126 **127A** **127B** (6)

An oxidation of biological importance is the formation of dopachrome, which is a precursor of eumelanin. *In vivo* dopachrome is the product of a rapid redox exchange between cyclodopa and its precursor dopaquinone (Scheme 23) (92MI2) (04MI1). The kinetics of the cyclodopa–dopachrome redox exchange and related systems have been studied *in vitro* using pulse radiolysis (85BBA49) (03PCR487).

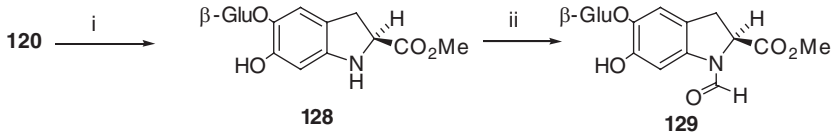
2. *Reaction at Nitrogen*

A number of *betanidin* analogues have been prepared by reaction of the methyl ester of cyclodopa **84** with suitably functionalized imine salts (75C527) (85HCA1670) (86HCA1588). A typical transformation is shown in Eq. (7) (75C527).



84 (7)

A variation of this procedure has been used to obtain cyclodopa 5-*O*-glucoside **128** from betanin **119** by base catalysed exchange with excess proline (Scheme 27) (84HCA1348). The glycoside is *N*-formylated (**128**→**129**) upon standing in dilute formic acid solution. Other *N*-acylation reactions have been discussed in Section IIIB (Scheme 20).



Reagents: i, aq. NH_3/proline; ii, aq. HCO_2H

Scheme 27

3. *Reaction at Oxygen*

The iodides **77** ($R^3 = R^4 = Me$, X = I) (Tables 4 and 5) have been obtained by reaction of the betaines **107** with methyl iodide in the presence of K_2CO_3.

4. *Reaction at Carbon*

Reaction of the methyl ester of cyclodopa **84** with potassium iodate, followed by reduction and acetylation gives the 7-iodo derivative **95** (R = Me) in good yield (Scheme 21) (77JOC4153). Under acidic conditions, the aromatic proton at position C-7 of cyclodopa **78** exchanges with deuterium (68HCA1476).

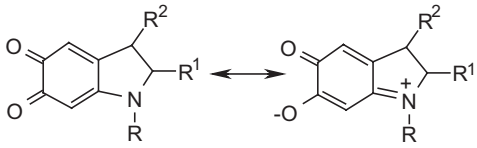
IV. 2,3-Dihydro-1*H*-indole-5,6-diones (Aminochromes)

2,3-Dihydroindole-5,6-diones have attracted considerable interest in biomedical circles because of their involvement in the pathways of melanogenesis and catecholamine oxidation. Chemically they are the *o*-quinones of 2,3-dihydro-5,6-dihydroxyindoles (indolines) (see Section III) and share several features in common with 4-amino-*o*-quinones, including an intense orange-to-red coloration, hence their common name "aminochromes" coined by Sobotka and Austin (51JA3077, 51JA5299). A comprehensive overview of the early chemistry is summarised in various reviews by Heacock (59CR181, 65AHC205) and Sobotka (57MI217), to which the reader is referred for a historical perspective. In the present survey, therefore, we will provide only a brief recapitulation of the early studies, focusing mainly on references from 1965 onwards.

In their classical paper, Green and Richter (37BJ596) assigned to adrenochrome the indolinequinone structure. However, due to its physical properties (red colour and solubility in water and polar solvents) and chemical reactivity (failure to form a phenazine derivative with *o*-phenylenediamine), Harley–Mason (48E307) argued that a "zwitterionic" *para*-quinonoid structure makes a large contribution to the resonance hybrid, whereby it has become customary to represent adrenochrome and other aminochromes in terms of the latter structure. Throughout this account, therefore, both canonical structures of aminochromes will be used.

The most investigated members of the series include adrenochrome (**63**, from the oxidative cyclization of adrenaline), dopachrome (**80**, from dopa), epinochrome

(**130**, from epinine) and dopaminochrome (**131**, from dopamine), while less attention has been focused on noradrenochrome (**132**, from noradrenaline) and *N*-isopropylnoradrenochrome **133**.



63, R=Me, R^1=H, R^2=OH
80, R=H, R^1=COOH, R^2=H
130, R=Me, R^1=R^2=H
131, R=R^1=R^2=H
132, R=R^1=H, R^2=OH
133, R=i-Pr, R^1=H, R^2=OH

A. Physical Properties

1. *General Properties*

Detailed accounts of the physical properties of aminochromes were given by Heacock (59CR181) (65AHC205). Adrenochrome **63**, epinochrome **130** and *N*-isopropylnoradrenochrome **133** may be obtained as stable crystalline solids, whereas the other aminochromes cannot be isolated because of their instability and have been characterized in solution. Adrenochrome is very soluble in water, methanol and ethanol, fairly soluble in acetonitrile, acetone, and DMF, but sparingly soluble in non-polar solvents (59CR181) (65AHC205). Halogenated adrenochromes are much less soluble in water. Noradrenochrome **132** is considerably less stable than adrenochrome **63**, as its solutions rapidly decompose to dark insoluble materials. *N*-Isopropylnoradrenochrome **133** is a purplish-red crystalline solid, whereas epinochrome **130** is a violet solid that rearranges even in the solid state.

2. *Ultraviolet Spectroscopy*

Several aminochromes have been characterized spectrophotometrically (65AHC205). They all display absorption maxima at around 205–215 nm and near 300 nm in the UV region, and also a less intense, broader absorption in the range 470–490 nm. Halogenation shifts the first absorption to *ca.* 230 nm and the visible band to *ca.* 520 nm.

The UV spectra of aminochrome semicarbazones have been extensively investigated. The main absorption maxima fall at *ca.* 360 nm at acidic and neutral pH, and shift to 435–460 nm in alkaline solution.

Table 6. Chemical shifts of proton and carbons of adrenochrome **63**

Position	2	3	4	5	6	7	8	9
δ^1H	3.64, 4.11	5.05	6.51			5.53		
δ^{13}C	64.87	66.58	127.83	186.30	173.83	93.08	161.96	156.35

3. *IR Spectroscopy*

The infrared spectra of isolable aminochromes have been reported previously (65AHC205). Complex absorption patterns can be observed in the "carbonyl" region, including intense bands in the range 1550–1600 cm^{-1} ascribed to the oxygenated function at C-6.

4. *NMR Spectroscopy*

In the previous review (65AHC205) no NMR data were reported for aminochromes due to the limited solubility of these compounds in suitable solvents. The only aminochrome for which NMR data are available is adrenochrome (Table 6) (88T6441).

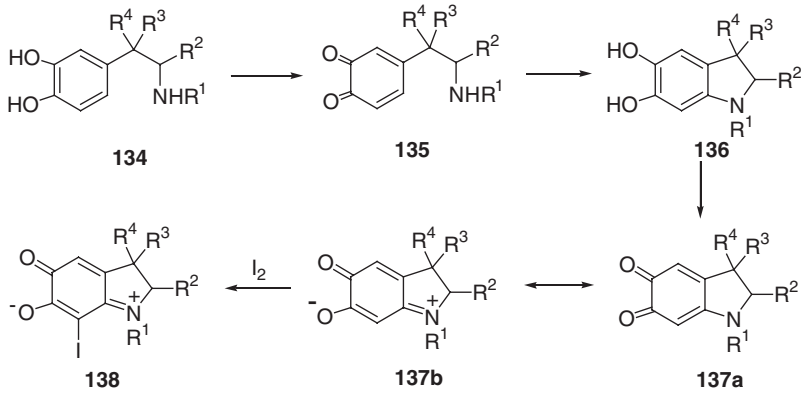
5. *Mass Spectrometry*

Mass spectrometric data for aminochromes have recently become available (01MI2466). Tandem mass spectrometry (MS/MS) fragmentation patterns were examined for five aminochromes. Although protonated aminochromes undergo similar fragmentation patterns with a characteristic consecutive loss of two carbonyl groups, the presence of different substituents led to significant changes in the collision-induced dissociation (CID) spectra. This feature is more evident for dopachrome, where the MS/MS spectrum is dominated by the loss of formic acid.

B. Preparation

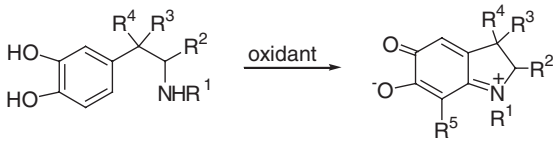
The most important preparative route to the aminochromes **137** is oxidation of primary or secondary catecholamines **134** (Scheme 28). Initial oxidation gives the *o*-quinones **135** that cyclize to the indoline **136** and further oxidation gives the aminochrome **137**. The 5,6-dihydroxyindolines **136** are not usually isolated, but for some studies mild oxidation of the previously isolated indoline (Section III) is a convenient preparative route (84TL2993).

A variety of oxidizing agents have been used to oxidize catecholamines to aminochromes and these include $K_3Fe(CN)_6$ (68HCA1476) (81CPB1935), $Ce(SO_4)_2$ (84TL2993), $NaIO_4$ (77JBC5729), MnO_2 (93JOC1607), Ph_2SeO (73SYN172), *p*-benzoquinone (70BCSJ2620), mushroom tyrosinase (77JBC5729) (84ABB438) (89CPB3386)), as well as the more usual Ag_2O and KIO_4 (see Table 7). In many of these studies the aminochrome is not isolated but studied or used in solution. In this



Scheme 28

Table 7. Preparation of aminochromes since 1965 <65AHC205>



Entry	R^1	R^2	R^3	R^4	R^5	Oxidant	M.p. (°C)	References
1	H	H	H	OH	H	Ag_2O	<105(d)	71CJC341
2	H	H	H	H	I	KIO_4	<106(d)	69CJC2009
3	H	H	Me	Me	H	Ag_2O	160–1	01JA9606
4	H	Me	H	OH	H	Ag_2O	<115(d)	73CJC776
5	Me	H	H	H	H	Ag_2O	80–3(d)	72CJC3360
6	Me	H	H	OH	H	Ph_2SeO	127(d)	73SYN172
7	Me	H	H	OMe	H	Ag_2O	81–6(d)	69CJC2009
8	Me	H	H	OEt	H	Ag_2O	79–81(d)	69CJC2009
9	Me	Me	H	OH	H	Ag_2O	<128(d)	69CJC2003
10	Me	H	H	OH	I	KIO_4	na	79ACSB244
11	Me	Me	H	OH	I	KIO_4	<96(d)	69CJC2003
12	Et	Me	H	OH	H	Ag_2O	<110(d)	69CJC2003
13	Et	Me	H	OH	I	KIO_4	<97 (d)	69CJC2003

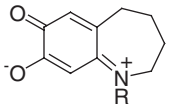
section, we restrict our survey primarily to aminochromes that have been isolated in crystalline form and fully characterized.

These are tabulated in Table 7. For a full survey Table 7 should be used in conjunction with Table 1 of the earlier Heacock survey (65AHC205). From Table 7 it can be seen that the most common oxidants are Ag_2O and KIO_4. However, it should be noted that yields of isolated aminochrome are often low (<30%). It is noteworthy that a rather good yield of adrenochrome (72%) (Entry 6) was obtained

by oxidation of L-adrenaline by diphenyl selenoxide (73SYN172). Only one example using this oxidant has been reported but it may be that this reagent, which avoids contamination and possible decomposition by silver, is a superior reagent to Ag_2O.

Use of potassium iodate as oxidant invariably results in formation of the 7-iodo aminochromes **138** (Table 7). These products are formed by electrophilic iodination of the initial product **137** by iodine (67CJC327) (67CJC1721) (67CJC2473) (73JA4261).

Dopachrome **80** is a particularly significant aminochrome because of its formation as an early intermediate in the biosynthesis of eumelanin. *In vivo* the dihydroindole **136** ($R^1 = R^3 = R^4 = H$, $R^2 = CO_2H$) is oxidized by its precursor (dopaquinone) to give dopachrome (see Section IIIB). *In vitro* dopachrome **80** has been generated in solution for numerous studies (70HCA1704) (72BASU2637) (76JCS(P2)1651) (77JBC5729) (82CPB2094) (84JCS(CC)1170) (85BBA49) (89CPB3386) (91JCS(F)2939) (03PCR487) but is too unstable to be isolated. Another aminochrome of particular interest because of its formation by oxidation of adrenaline is adrenochrome **63** (Table 7, entry 6). In addition to the preparation cited in Table 7, a number of workers have generated and studied adrenochrome in solution without isolation (69MI50) (76CJC3815) (81CPB1935) (86G423) (86JCS(D)1833) (93JCS(P2)2435).



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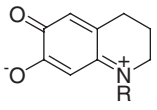


140

It is noteworthy that the higher homologues **139** (R = nPr, iPr, $CH_2CF_2CF_3$) have been prepared as purple solids by oxidation of the corresponding catechols (03OBC3120). We are not aware of any reports of the isolation of examples of the six-membered analogues **140**. However, the derivative **140** (R = nPr) has been detected in solution as the final product of tyrosinase oxidation of the corresponding catechol (03PCR397).

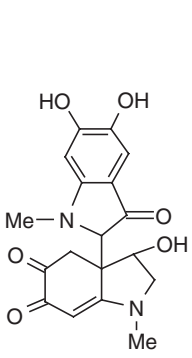
C. Reactions

Due to their nature as *o*-quinones bearing an electron-donating amino group, aminochromes are susceptible to (i) reduction, to give the corresponding indolines; (ii) addition of various nucleophiles, e.g. thiols, bisulphite and amines; (iii) electrophilic substitution (e.g. halogenation); (iv) complex formation with metal ions; and (v) photochemical degradation (79PP479). However, the majority of the studies of aminochrome chemistry have been focused on the rearrangement reaction, leading to 5,6-dihydroxyindoles. Mechanistically this reaction is an isomerization, which consists of a sequence of proton shifts from the 2- and 3-positions of the indole ring, and is driven by the higher thermodynamic stability of the resulting 5,6-dihydroxyindole derivative. The elusive character of the aminochromes and their unfavorable properties, along with the lack of adequate physicochemical

methodologies, account for the many mechanistic uncertainties of the early studies (65AHC205). During the last decades, however, with the advent of modern spectral techniques, several important insights have been gained that have provided an improved picture of the rearrangement reaction and other aspects of aminochrome chemistry. In the following subsections, the reactivity of the most representative aminochromes is discussed case by case.

1. *Adrenochrome (**63**)*

a. Isomerization. Isomerization of adrenochrome **63** by alkali leads to the intensely yellow-green fluorescent 3,5,6-trihydroxy-1-methylindole (adrenolutin, **4**). Compound **4** can be isolated by acidification of the mixture followed by recrystallization in the presence of sodium hydrosulphite. The same isomerization product is formed when adrenochrome is treated with Zn^{2+} and other metal cations (89BBA297). The reaction is promoted by coordination of the metal to the *o*-dicarbonyl function inducing proton shift. At neutral pH, and in the absence of oxygen, adrenochrome changes into an unusual dimerization product which has been identified as compound **141** (88T6441). Such a dimer conceivably arises by the nuclephilic attack of a 3,5,6-trihydroxyindole intermediate, i.e. the enol tautomer of adrenolutin **4**, to the angular 9-position of the aminochrome.



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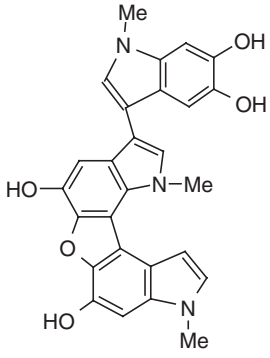


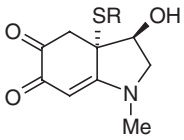
142

At acidic pH adrenochrome **63** is slowly converted into a black pigment, originally referred to as adrenaline black. Pigment formation proceeds through a number of oligomer intermediates that were isolated and identified as two 2,3′-linked biindolyls and the 4,7′:3′,3″-linked trimer **142** (88T1803).

b. Reduction. Reduction with various agents, including hydrogen over a catalyst, ascorbic acid (65JCS4728), sodium borohydride, thiol compounds, as well as ferrous ions, leads to 5,6-dihydroxy-1-methylindole **3**. The reaction involves reduction of the aminochrome to 2,3-dihydro-3,5,6-trihydroxyindole followed by a dehydration step. The electrochemical reduction of adrenochrome on a glassy carbon electrode was studied by a.c. impedance in various buffered solutions. The plots of impedance on

the complex plane were semicircles rotated clockwise around the origin in higher frequencies (99JES256).

c. Reaction with Nucleophiles. A systematic investigation of the reactions of various aminochromes with thiol compounds was reported by Powell and co-workers (69CJC467, 73JCS(P1)509). Identified products included 5,6-dihydroxyindoles, 4-alkylthio-5,6-dihydroxyindoles, and relatively unstable adducts. Upon reaction with thiol compounds adrenochrome undergoes reduction to indole **3** and/or nucleophilic addition to give mixtures of adducts with a keto group at C-5. Thus, *N*-acetylcysteine, thioglycolic acid and *β*-mercaptopropionic acid gave adducts of the type **143** at the 9- (or 3a)-position that could be stabilized through conversion to the corresponding hydrazones or semicarbazones (81CPB1935). Stereochemical characterization indicates that the preferred mode of attack is from the opposite side to the OH group, to give the *anti*-adducts, whereas at 5 °C *β*-mercaptopropionic acid reacted to give the *syn*-adduct.



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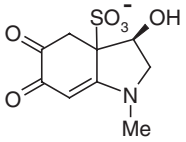


144

7-Iodoadrenochrome reacts with glutathione to give 5,6-dihydroxy-7-iodo-1-methylindole, 5,6-dihydroxy-1-methylindole **3**, 7-*S*-glutathionyl-5,6-dihydroxy-1-methylindole, and a trace of a product that is probably 4-*S*-glutathionyl-5,6-dihydroxy-7-iodo-1-methylindole (66CJC565). It reacts with the monosodium salt of glutathione to give mainly 5,6-dihydroxy-7-iodo-1-methylindole and 4-*S*-glutathionyl-5,6-dihydroxy-7-iodo-1-methylindole, with smaller quantities of 7-*S*-glutathionyl-5,6-dihydroxy-1-methylindole and 5,6-dihydroxy-1-methylindole. 7-Bromoadrenochrome reacts with glutathione (free acid or monosodium salt) to give mainly 7-bromo-5,6-dihydroxy-1-methylindole and a second product, which is probably 7-bromo-4-*S*-glutathionyl-5,6-dihydroxy-1-methylindole. Product formation was proposed to involve direct reduction of the aminochrome and addition of the thiol compound to the α,β-unsaturated C5-carbonyl system.

Addition products are likewise formed by the reaction of adrenochrome with sodium bisulphite (71CI1021). The main adduct has been characterized by NMR and shown to bear a sulphonate group at the 9-position (**144**). No evidence for the enol tautomer was obtained. The preferential reactivity of adrenochrome through the 9-position is also reflected in the structure of the dimer **141** obtained under anaerobic conditions (88T6441).

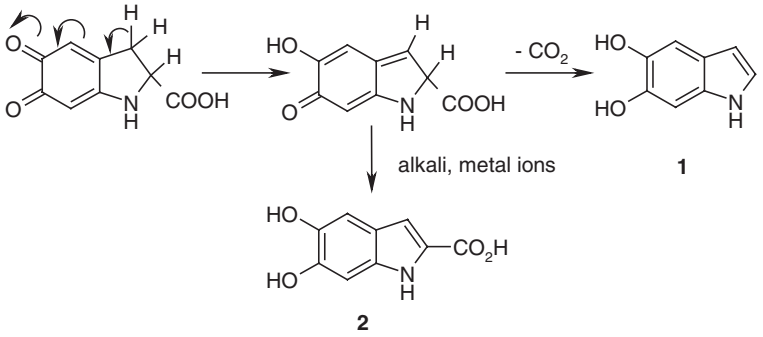
Adrenochrome reacts with amines and hydrazides to give mainly condensation products at C-5 (59CR181) and, in the case of ethylenediamine, 2,3-dihydro-3-hydroxy-1-methylpyrrolo [4,5-*g*] quinoxaline (59T70). A detailed account of the latter reaction has been given in a previous review (65AHC205).

d. Photochemical Degradation. The generation of aminochromes by irradiation of adrenaline and other catecholamines with UV radiation at 254 nm has been described (79PP479). In the same study, quantum yields for the photodegradation of adrenochrome and other aminochromes were also determined. The methylene blue-sensitized photooxidation of adrenochrome was studied by steady-state kinetics (91MI117). During irradiation, disappearance of adrenochrome and the formation of adrenochrome-melanin was observed. Mechanistic analysis suggested the participation of two types of photosensitized mechanisms, one (type II) predominating at pH <9 and involving singlet oxygen, and the other (type I) at $>$pH 9.

2. *Dopachrome (**80**)*

a. Isomerization. With very few exceptions, studies of the chemistry of dopachrome **80** have been focused on the isomerization reaction, which represents the branching point and the rate-determining step in the biosynthesis of melanins. This reaction displays a pH-dependent kinetic profile, with a minimum rate at pH$\sim$5, and may proceed with or without decarboxylation to give 5,6-dihydroxyindoles **1** and/or **2**, respectively. In particular, the latter route prevails at acidic or alkaline pH. The mechanism of dopachrome rearrangement has been the focus of much attention and controversy. Isotopic labelling and model studies (90TL6095) (91TL3849) (91JBC6073) eventually showed that the reaction involves abstraction of a proton at the 3-position and formation of a quinomethane intermediate which is then converted to indoles **1** or **2** (Scheme 29) depending on factors such as the pH of the medium and the presence of metal ions, e.g. Zn^{2+}, Cu^{2+}, Al^{3+} (85G357) (87BBA203) (03MI3075) (03MI1689). This mechanism was confirmed by a study of the aminochrome **145**, formed from α-methyl-3,4-dihydroxyphenylalanine ethyl ester, which leads to the quinomethane intermediate **146** (Eq. (8)) (90TL6095).

At pH 7.4 metal ions promote the non-decarboxylative pathway to the acid **2**, most likely by enhancing the acidity of the H-2 proton (87BBA203). Notably, however, at pH 5.5, aluminium ions promote the rapid decarboxylative rearrangement of dopachrome leading to 5,6-dihydroxyindole **1** rather than the acid **2** (03MI1689).



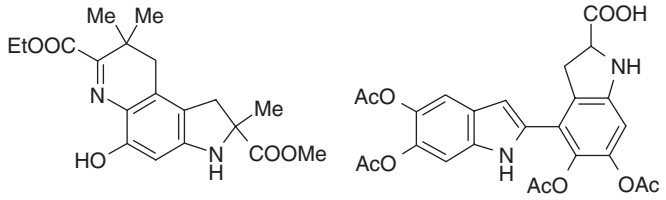
Scheme 29

145 146 (8)

In mammalian melanocytes, an enzyme termed *dopachrome tautomerase* exerts the same effect as metal ions in promoting the non-decarboxylative rearrangement to the acid **2** (85JID229) (91BJ393) (91BBA1204) (94BBA53). Dopachrome tautomerase was discovered by Pawelek in 1980 (80NAT617) (90BBRC1328) (92FEBS126) and was originally designated dopachrome rearranging factor (DRF). More recently, it has also been referred to as tyrosinase-related protein 2 (TRP-2) (92EJ519). The enzyme catalyses specifically the rearrangement of L-dopachrome and its methyl ester to the acid **2** and its ester, but does not act on D-dopachrome, α-methyldopachrome, dopaminochrome, and adrenochrome. In invertebrates, enzymatic activities have been described that promote the decarboxylative rearrangement of dopachrome to 5,6-dihydroxyindole **1** (94BJ839) (02BJ333).

b. Reduction. Dopachrome methyl ester was reduced by sodium dithionite to give leucodopachrome methyl ester (68HCA1476). The product is unstable and was isolated as the acetyl derivative.

c. Reactions with Nucleophiles. In the presence of sulphydryl compounds, e.g. glutathione, dopachrome forms addition products such as 4-*S*-glutathionyl-5,6-dihydroxyindole (87T5357). The analogous reaction of cysteine ethyl ester with methyldopachrome methyl ester furnished an unusual adduct containing the 1,2-dihydro-3*H*,8*H*-pyrrolo[2,3-*h*][1,4]benzothiazine ring system **147**.



147 148

Addition of 5,6-dihydroxyindole **1** to dopachrome may occur during rearrangement and leads to a product that has been identified after reduction and acetylation as compond **148** (87G627).

When generated *in situ* by oxidation of an alcoholic solution of leucodopachrome methyl ester in the air, dopachrome reacts with semicarbazide to give a monosemicarbazone at C-5 (68HCA1476).

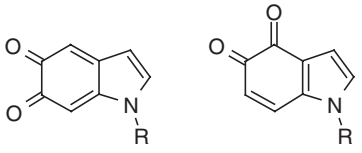
3. *Dopaminochrome (**131**)*

a. Isomerization and Reduction. Dopaminochrome **131** isomerizes to 5,6-dihydroxyindole **1** (93BC392) but the reaction is relatively slow compared to that of dopachrome **80**. Dopaminochrome reduction leads to 5,6-dihydroxy-2,3-dihydroindole, and the subject has been the focus of interest in relation to the mechanisms of neurodegeneration (97JMC2211) (01NR157) (04ND468).

b. Reactions with Nucleophiles. Although the direct reaction of dopaminochrome **131** with thiol compounds has not yet been investigated, the reductive conjugation with glutathione mediated by glutathione transferases (GSTs) has been reported (97JBC5727) (97BJ25). The product of the conjugation displayed a UV spectrum with absorption peaks at 277 and 295 nm and has been identified as 4-*S*-glutathionyl-5,6-dihydroxyindoline by NMR spectroscopy. In contrast to reduced forms of aminochrome (leucoaminochrome and *o*-semiquinone), 4-*S*-glutathionyl-5,6-dihydroxyindoline is stable in the presence of oxygen, superoxide radicals, and hydrogen peroxide. On oxidation, it is converted to 4-*S*-glutathionyl dopaminochrome, with an absorption peak at 620 nm.

V. Indole-5,6-diones

Indole-5,6-diones (or 5,6-indolequinones) **149** are among the most elusive and enigmatic quinones found in nature because of their marked instability, resembling that of 2,3-naphthoquinones. This is a consequence of the incompatibility of the dione moiety at the 5,6-positions with the aromatic pyrrole ring, which makes it impossible to write neutral canonical resonance structures with the pyrrole moiety bearing an aromatic sextet (cf. **149** and **150**). Unlike 4,5-indolequinone **150** (R = H), which is a stable crystalline solid (56CB489), 5,6-indolequinones **149** are hardly detectable and for a long time even their existence as independent intermediates in the oxidation of 5,6-dihydroxyindoles was more a matter of surmise than of direct proof. Omitting more than passing reference to the early literature on the presumptive identification of 5,6-indolequinones by spectrophotometric techniques, in the following section the focus will be restricted to those modern studies in which the involvement of 5,6-indolequinones **149** is either certain or highly likely. Because of the virtual lack of literature dealing with authentic preparative procedures, with a single noticeable exception (96TL4241) detailed below, a "Preparation" sub-section has not been included in Section V.



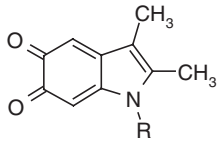
149 **150**

A. Physical Properties

1. *Spectroscopic Properties*

The spectrophotometric characterization of transient oxidation products of 5,6-dihydroxyindoles has been reported in Section IIC1a, and the possible identity with 5,6-indolequinones **149** of some of the transient species detected in the decay (disproportionation) of semiquinones has been discussed. The first direct spectral insight into 5,6-indolequinones **149** came in 1996 when the generation and spectral characterization of 2,3-dimethyl-5,6-indolequinone **151** was reported (96TL4241). Oxidation of 2,3-dimethyl-5,6-dihydroxyindole **25** with *o*-chloranil in CD_3OD resulted in the disappearance of the starting material and the development of a yellow species. The UV spectrum showed a maximum centred at 360 nm. This chromophore is ipsochromically shifted with respect to the early predictions: see, for example, the alleged identification of the purple pigment "melanochrome" ($\lambda_{max} = 540$ nm) with 5,6-indolequinones by Mason (48JBC83).

The ^{1}H-NMR spectrum of quinone **151** displayed two singlets at δ 5.47 and 6.26 (1H each) and the signals for the methyl groups at δ 1.47 and 2.02. On standing, this species gradually decomposed to melanin-like materials, which hampers a more complete characterization by spectroscopic techniques.



151

2. *Computational Studies*

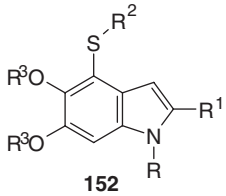
The results of quantum mechanical calculations on indole-5,6-diones, together with those on 5,6-dihydroxyindoles, are covered in Section IIA2.

B. Reactions

As mentioned above, the direct investigation of the reactivity of 5,6-indolequinones **149** is a difficult task and most of what is known derives from studies of the oxidation of 5,6-dihydroxyindoles in the presence of nucleophiles as trapping agents. These studies form the core of this section. In fact, the oxidative polymerization of 5,6-dihydroxyindoles itself might be taken as reflecting the reactivity of 5,6-indolequinones versus 5,6-dihydroxyindoles, which has been addressed in a previous section.

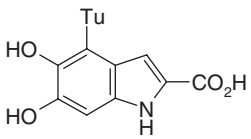
Oxidation of indoles **1**, **2** or **3** with tyrosinase in the presence of cysteine or glutathione leads to the formation of the corresponding 4-*S*-conjugates **152** as the major products (87T5351) (88PCR48) (91JOC1767). Oxidation of the acid **2** in the

presence of thiouracil gives adducts at C-4 (**153**), which are also incorporated in oligomeric scaffolds (96JMC5192). Notably, however, the same reaction carried out on 5,6-dihydroxyindole **1** proceeds with different regiochemistry leading to adducts at the 4- as well as the 2- and 3-positions **154**.



152

R = H, Me
R^1 =H, COOH
R^2 =cysteinyl or glutathionyl
R^3 =OH, Ac



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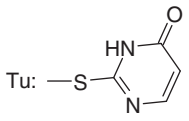
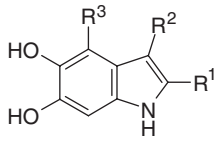


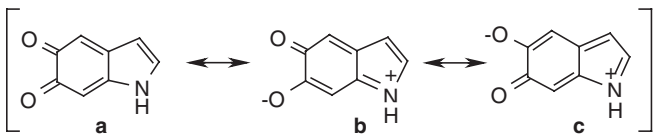
Tu:



154

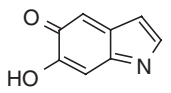
a, R^1=Tu, R^2=R^3=H
b, R^1=R^3=H, R^2=Tu
c, R^1=R^2=H, R^3=Tu

The different behaviour of thiols and thiones with 5,6-indolequinone bears considerable resemblance to the dichotomy observed in the addition of these nucleophiles to *o*-quinones (90BBA221) (97MR478). In particular, the pattern of reactivity of thiouracil may be taken to indicate a relatively high electron deficiency on the 5,6-indolequinone pyrrole moiety. This observation is in agreement with another study showing that azide ions add to 5,6-indolequinone to give a hypothetical adduct at C-2 which could evolve to give a triazole derivative (92TL3045), which is difficult to rationalize in terms of the classical structural formulation of this quinone. A plausible explanation envisages either a substantial contribution of dipolar resonance hybrids, e.g. **149b** and **149c**, to the structure or a tautomerism leading to quinomethane-like species, e.g. **7** and **9**.



a **b** **c**

149



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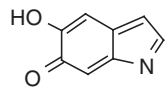

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VI. Biological Perspectives and the Problem of Melanin Structure

Indoles occupy an important place in biological chemistry. However, from the biological perspective perhaps the most significant aspect of the oxidative synthesis of indoles lies in the evolutionary value of the pigment melanin. The detailed structure of melanin is unknown but the basic structure of eumelanin (the black-brown pigment) entails a backbone of 5,6-dioxyindole moieties that contain both quinone and hydroquinone residues (92MI2) (97T8281). As shown in the introductory section (Scheme 1), the biosynthetic route to eumelanin involves the enzymatic oxidation of tyrosine, or related congeners such as 3,4-dihydroxyalanine (dopa), to the corresponding *o*-quinone followed by intramolecular cyclization to give rise to the indoline which, on further oxidation and tautomerization involving aromatization of the five-membered ring, yields 5,6-dihydroxyindole **1**. This efficient oxidative route to indole derivatives, often referred to as the Raper–Mason pathway, has been evolutionarily strongly conserved. An interesting aspect of this pathway is the intercession of a tautomerase enzyme that appears to have other (unclear) functions as a macrophage migration inhibitory factor (99CMB1035) and includes phenylpyruvate tautomerase activity in the liver (97MR517). The generation of 5,6-dihydroxyindole **1** may have physiological significance and may play an important role in photoprotection (95PP650). Indolic melanin precursors have been shown to possess redox properties that may modify some important processes such as radical attack on biomolecules. For example, 5,6-dihydroxyindole **1** (and 5,6-dihydroxyindole-2-carboxylic acid, **2**) have been shown to inhibit lipid peroxidation (93BBA175) (97BBA61) and are good scavengers for peroxynitrite and hydroxyl radicals generated by the Fenton reaction (98BBA27) (99CRT985).

However, because of the cytotoxic action of several precursors, the biosynthesis of melanin has been considered a hazard for pigment cells and, in vertebrates, melanogenesis takes place in sequestered intracytoplasmic organelles in the presence of a stromal protein matrix. This may impose constraints on the orientation of the indole moieties which may be important in conferring special physicochemical properties on the melanin produced. Other relevant factors include the incorporation of cysteine in the synthetic pathway resulting in inclusion of benzothiazine moieties in the class of yellow-red pigments known as phaeomelanins. The final steps in pigment formation are not well understood but at least some degree of polymerization of indole-5,6-quinone seems to be involved (90BBA319).

Although the precise arrangement of the components of melanin remains to be determined a degree of conjugation exists in the polymer, which embues eumelanin with strong photon absorption in the visible and ultraviolet spectrum. Some recent calculations (03JPC(B)3061) (03JPC(B)11558) suggest that oligomers of dihydroxy-indole possess strong photon absorbance properties. The degree of conjugation between rings is sufficient to permit the lowering of the quantal energies required for light absorption when the pigment is oxidized. This bathochromic characteristic of melanin (85PTRSL679) results in significant photon absorption even in the infra-red portion of the spectrum. This may permit it to act as a means of thermal absorption in poikilotherms (e.g. snakes and lizards) and for animals in cold climates where solar radiation constitutes a significant factor in energy conservation.

Photoprotection is widely considered to be the most significant action of melanin in humans, and there is good evidence that increased epidermal melanization is associated with a significantly decreased risk of skin cancer related to sun exposure. The mechanism may involve the absorption of energetic photons that might damage important cellular structures such as DNA, and therefore constitutes an aspect of screening. Alternatively, the protective action may involve the generation of free radicals that are toxic to cells which have been exposed to potentially genotoxic doses of light (74MI1104). Because of the conjugated structure of melanin there is an equilibrium between the quinone and hydroquinone moieties in the polymer, which renders the pigment a facile electron exchanger. It can, thus, act as a free radical generator or scavenger (87CBF123). The facile formation of indole semiquinones results in melanins being stabilised free radicals. The free radical content of melanin in suspension at neutral pH has been estimated to be around 2×10^{18} spins/g (84MI67).

Another factor is the relatively high density of negative surface charge on melanin which renders it a cation trap (73MI203) and it has been suggested that this constitutes one of the biological benefits conferred by surface pigment since, by transfer of melanin to epidermal cells which are desquamated, melanin provides an excretory pathway for metals and other cationic materials (97B408). Of course, these binding properties may also pose a biological hazard, e.g. by retention of potentially toxic materials in sites where pigment is not subject to turnover, such as in the eye and the inner ear (05MI3).

Overall, the generation and distribution of surface pigments based on the 5,6-dihydroxyindole structure is clearly associated with survival benefit, perhaps including its role in camouflage or sexual display as well as radiation protection. Animals in which melanogenesis is deficient or absent (as in albinism) appear to be disadvantaged.

REFERENCES

27BJ89 H. S. Raper, *Biochem. J.*, **21**, 89 (1927).
32JCS546 H. Burton, *J. Chem. Soc.*, 546 (1932).
32JCS789 R. Robinson and S. Sugasawa, *J. Chem. Soc.*, 789 (1932).
32LA22 C. Schöpf and K. Thierfelder, *Liebigs Ann. Chem.*, **497**, 22 (1932).
37BJ596 D. E. Green and D. Richter, *Biochem. J.*, **31**, 596 (1937).
48E307 J. Harley-Mason, *Experientia*, **4**, 307 (1948).
48JBC83 H. S. Mason, *J. Biol. Chem.*, **172**, 83 (1948).
48JCS1244 J. Harley-Mason, *J. Chem. Soc.*, 1244 (1948).
48JCS2223 R. J. S. Beer, K. Clarke, H. G. Khorana, and A. Robertson, *J. Chem. Soc.*, 2223 (1948).
48NAT525 R. J. S. Beer, K. Clarke, H. G. Khorana, and A. Robertson, *Nature*, **161**, 525 (1948).
48NAT725 H. Burton and J. A. Duffield, *Nature*, **161**, 725 (1948).
49JCS78 H. Burton and J. A. Duffield, *J. Chem. Soc.*, 78 (1949).
49JCS2061 R. J. S. Beer, L. McGrath, A. Robertson, and A. B. Woodier, *J. Chem. Soc.*, 2061 (1949).
50JA1062 H. Burton, J. A. Duffield, and P. F. G. Praill, *J. Am. Chem. Soc.*, **72**, 1062 (1950).

50JCS1276 J. Harley-Mason, *J. Chem. Soc.*, 1276 (1950).
50NAT1036 J. Harley-Mason and J. D. Bu'Lock, *Nature*, **166**, 1036 (1950).
51JA3077 H. J. Sobotka and J. Austin, *J. Am. Chem. Soc.*, **73**, 3077 (1951).
51JA5299 J. Austin, J. D. Chanley, and H. J. Sobotka, *J. Am. Chem. Soc.*, **73**, 5299 (1951).
51JCS2248 J. D. Bu'Lock and J. Harley-Mason, *J. Chem. Soc.*, 2248 (1951).
51JCS2426 R. J. S. Beer, J. P. Brown, and A. Robertson, *J. Chem. Soc.*, 2426 (1951).
52NAT618 J. Ewing, G. Hughes, E. Ritchie, and W. C. Taylor, *Nature*, **169**, 618 (1952).
53HCA708 R. W. Balsiger, R. W Fischer, R. Hirt, and E. Giovannini, *Helv. Chim. Acta*, **36**, 708 (1953).
53JA5887 C. F. Huebner, H. A. Troxell, and D. C. Schroeder, *J. Am. Chem. Soc.*, **75**, 5887 (1953).
53JCS200 J. Harley-Mason, *J. Chem. Soc.*, 200 (1953).
53JCS3525 R. I. T. Cromartie and J. Harley-Mason, *J. Chem. Soc.*, 3525 (1953).
54JCS1947 R. J. S. Beer, T. Broadhurst, and A. Robertson, *J. Chem. Soc.*, 1947 (1954).
55JA3844 G. N. Walker, *J. Am. Chem. Soc.*, **77**, 3844 (1955).
56CB489 H. J. Teuber and G. Staiger, *Chem. Ber.*, **89**, 489 (1956).
56JA3698 G. N. Walker, *J. Am. Chem. Soc.*, **78**, 3698 (1956).
57JOC331 R. D. Morin, F. Benington, and L. C. Clark Jr., *J. Org. Chem.*, **22**, 331 (1957).
57MI217 H. J. Sobotka, N. Barsel, and J. D. Chanley, *Fortschr. Chem. Org. Naturst.*, **14**, 217 (1957).
58NAT526 R. A. Heacock and B. D. Laidlaw, *Nature*, **182**, 526 (1958).
59CR181 R. A. Heacock, *Chem. Rev.*, **59**, 181 (1959).
59JA6231 S. Senoh and B. Witkop, *J. Am. Chem. Soc.*, **81**, 6231 (1959).
59T70 J. Harley-Mason and A. H. Laird, *Tetrahedron*, **7**, 70 (1959).
60ABB231 H. C. Longuet-Higgins, *Arch. Biochem. Biophys.*, **86**, 231 (1960).
61BBA384 A. Pullman and B. Pullman, *Biochim. Biophys. Acta*, **54**, 384 (1961).
61CJC231 R. A. Heacock, M. E. Mahon, and B. D. Scott, *Can. J. Chem.*, **39**, 231 (1961).
62HCA638 H. Wyler and A. S. Dreiding, *Helv. Chim. Acta*, **45**, 638 (1962).
62HCA640 T. J. Mabry, H. Wyler, G. Sassu, M. Mercier, I. Parikh, and A. S. Dreiding, *Helv. Chim. Acta*, **45**, 640 (1962).
62JOC507 T. E. Young, *J. Org. Chem.*, **27**, 507 (1962).
63JA1825 R. A. Heacock, O. Hutzinger, B. D. Scott, J. W. Daly, and B. Witkop, *J. Am. Chem. Soc.*, **85**, 1825 (1963).
64BJ471 M. S. Blois, A. B. Zahlan, and J. E. Maling, *Biophys. J.*, **4**, 471 (1964).
64CJC484 G. L. Mattok and R. A. Heacock, *Can. J. Chem.*, **42**, 484 (1964).
64CJC1401 G. L. Mattok and R. A. Heacock, *Can. J. Chem.*, **42**, 1401 (1964).
65AHC205 R. A. Heacock, *Adv. Heterocycl. Chem.*, **5**, 205 (1965).
65JCS4728 G. L. Mattok, *J. Chem. Soc.*, 4728 (1965).
65JHC387 J. D. Benigni and R. L. Minnis, *J. Heterocycl. Chem.*, **2**, 387 (1965).
66CJC565 G. L. Mattok and R. A. Heacock, *Can. J. Chem.*, **44**, 565 (1966).
67AGE799 B. Franck and L. -F. Tietze, *Angew. Chem. Int. Ed.*, **6**, 799 (1967).
67CJC327 G. L. Mattok and D. L. Wilson, *Can. J. Chem.*, **44**, 327 (1967).
67CJC1721 G. L. Mattok and D. L. Wilson, *Can. J. Chem.*, **44**, 1721 (1967).
67CJC2473 G. L. Mattok and D. L. Wilson, *Can. J. Chem.*, **44**, 2473 (1967).
67JA447 M. D. Hawley, S. V. Tatwawadi, S. Piekarski, and R. N. Adams, *J. Am. Chem. Soc.*, **89**, 447 (1967).
67JPS1019 R. E. Counsell, T. O. Smith, J. Doelle, D. Meier, and W. H. Beierwalter, *J. Pharm. Sci.*, **56**, 1019 (1967).

67NAT190 P. A. Riley, *Nature*, **213**, 190 (1967).

68B3089 W. H. Harrison, W. W. Whisler, and B. J. Hill, *Biochemistry*, **7**, 3089 (1968).

68HCA1476 H. Wyler and J. Chiovini, *Helv. Chim. Acta*, **51**, 1476 (1968).

68MI1 R. A. Nicolaus, Melanins, Hermann, Paris (1968).

68NKZ760 Y. Omote, Y. Fujinuma, K. -T. Kuo, and N. Sugiyama, *Nippon Kagaku Zasshi*, **87**, 760 (1968).

69CJC467 W. Powell, R. A. Heacock, G. L. Mattok, and D. L. Wilson, *Can. J. Chem.*, **47**, 467 (1969).

69CJC2003 O. Hutzinger and R. A. Heacock, *Can. J. Chem.*, **47**, 2003 (1969).

69CJC2009 R. A. Heacock and O. Hutzinger, *Can. J. Chem.*, **47**, 2009 (1969).

69MI50 H. J. Roth and U. Volkmann, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **302**, 434 (1969).

70BCSJ2620 A. Hikosaka and J. Kumanotani, *Bull. Chem. Soc. Japan*, **43**, 2620 (1970).

70G693 G. Piattelli-Oriente, S. Sciuto, and M. Piattelli, *Gazz. Chim. Ital.*, **100**, 693 (1970).

70HCA1704 U. Wölcke, A. Kaiser, W. Koch, and M. Scheer, *Helv. Chim. Acta*, **53**, 1704 (1970).

70JCS(C)865 R. F. Chapman and G. A. Swan, *J. Chem. Soc., (C)*, 865 (1970).

70MC161 H. Hemetsberger, D. Knittell, and H. Weidmann, *Monatschefie fur Chemie*, **101**, 161 (1970).

71CI1021 R. A. Heacock, R. Marchelli, and W. S. Powell, *Chem. Ind.*, 1021 (1971).

71CJC341 W. S. Powell and R. A. Heacock, *Can. J. Chem.*, **49**, 341 (1971).

72BASU2637 G. N. Bogdanov and V. N. Shtol'ko, Bull. Acad. Sci. USSR, *Div. Chem. Soc. (Eng. Transl.)*, 2637 (1972).

72CJC3360 W. S. Powell and R. A. Heacock, *Can. J. Chem.*, **50**, 3360 (1972).

73CJC776 W. S. Powell, R. A. Heacock, D. G. Smith, and A. G. McInnes, *Can. J. Chem.*, **51**, 776 (1973).

73CPB1839 A. Brossi, A. Ramel, J. O'Brien, and S. Teitel, *Chem. Pharm. Bull.*, **21**, 1839 (1973).

73JA4261 E. Grovenstein Jr., N. S. Aprahamian, C. J. Bryan, N. S. Gnanapragasam, D. C. Kilby, J. M. McKelvey Jr., and R. J. Sullivan, *J. Am. Chem. Soc.*, **95**, 4261 (1973).

73JCS(P1)509 W. S. Powell and R. A. Heacock, *J. Chem. Soc., Perkin Trans. 1*, 509 (1973).

73MI203 J. Horcicko, J. Borovansky, J. Duchon, and B. Prochzkova, *Hoppe-Seyler's Z. Physiol. Chem.*, **354** (1973).

73MI424 R. Livingstone, in *"Rodd's Chemistry of Organic Compounds"* (S. Coffey ed.), Vol. IVA, p. 424, Elsevier, Amsterdam (1973).

73SYN172 K. Balenović, N. Bregant, and I. Perina, *Synthesis*, 172 (1973).

74AC305 R. H. Thomson, *Angew. Chem. Int. Ed. Engl.*, **13**, 305 (1974).

74BJ207 S. Ito and J. A. C. Nicol, *BioChem. J.*, **143**, 207 (1974).

74CJC1019 W. S. Powell and R. A. Heacock, *Can. J. Chem.*, **52**, 1019 (1974).

74FCON522 G. A. Swan, *Fortschr. Chem. Org. Naturst.*, **31**, 522 (1974).

74JOC1980 T. E. Young, J. R. Griswold, and M. H. Hulbert, *J. Org. Chem.*, **39**, 1980 (1974).

74MI1104 P. A. Riley, Melanin and Melanocytes, in *"The Physiology and Pathophysiology of the Skin"* (A. Jarrett ed.), Vol. 3, p. 1104, Academic Press, London (1974).

75C527 M. Siegfried, *Chimia*, **29**, 527 (1975).

76CJC3815 M. S. Rahaman and S. M. Korenkiewicz, *Can. J. Chem.*, **54**, 3815 (1976).

76END32 G. Prota and R. H. Thomson, *Endeavour*, **35**, 32 (1976).
76JCS(P1)339 G. A. Swan, *J. Chem. Soc., Perkin Trans. 1*, 339 (1976).
76JCS(P2)1651 E. Pelizzetti, E. Mentasti, and E. Pramauro, *J. Chem. Soc., Perkin Trans. 2*, 1651 (1976).
77JBC5729 D. G. Graham and P. W. Jeffs, *J. Biol. Chem.*, **252**, 5729 (1977).
77JOC4153 G. Büchi and T. Kamikawa, *J. Org. Chem.*, **42**, 4153 (1977).
78JMC548 C. G. Chavdarian, D. Karashima, N. Castagnoli, and H. K. Hundley, *J. Med. Chem.*, **21**, 548 (1978).
78MI190 R. A. Nicolaus, *Metodicum Chimicum*, G. Thieme, Stuttgart, **11**, 190 (1978).
79ACS(B)244 A. M. Opheim, *Acta Chem. Scand., B*, **33**, 244 (1979).
79PP479 N. J. De Mol, G. M. J. Beijersbergen van Henegouwen, and K. W. Gerritsma, *Photochem. Photobiol.*, **29**, 479 (1979).
80JID122 G. Prota, *J. Invest Dermatol.*, **75**, 122 (1980).
80JOC2899 T. E. Young, B. W. Babbitt, and L. A. Wolfe, *J. Org. Chem.*, **45**, 2899 (1980).
80NAT617 J. Pawelek, A. Korner, A. Bergstrom, and J. Bolognia, *Nature*, **286**, 617 (1980).
80PA223 P. A. Riley, *Pathobiol. Ann.*, **10**, 223 (1980).
80SYN663 I. K. Stamos, *Synthesis*, 663 (1980).
81CPB1935 E. Kato, M. Oya, K. Uda, T. Iso, T. Fujita, and J. -I. Iwao, *Chem. Pharm. Bull.*, **29**, 1935 (1981).
81PP423 C. C. Felix and R. C. Sealy, *Photochem. Photobiol.*, **34**, 423 (1981).
82CPB2094 N. Motohashi, H. Eguchi, and I. Mori, *Chem. Pharm. Bull.*, **30**, 2094 (1982).
82JMC263 R. T. Borchardt and P. Bhatia, *J. Med. Chem.*, **25**, 263 (1982).
82JOC5258 A. C. Cheng, A. T. Shulgin, and N. Castagnoli Jr., *J. Org. Chem.*, **47**, 5258 (1982).
83JOC562 T. E. Young and B. W. Babbitt, *J. Org. Chem.*, **48**, 562 (1983).
83JOC3347 A. K. Sinhababu and R. T. Borchardt, *J. Org. Chem.*, **48**, 3347 (1983).
84ABB438 M. Jimenez, F. Garcia-Carmona, F. Garcia-Canovas, J. L. Iborra, J. A. Lozano, and F. Martinez, *Arch. Biochem. Biophys.*, **235**, 438 (1984).
84HCA1348 H. Wyler, U. Meuer, J. Bauer, and L. Stravs-Mombelli, *Helv. Chim. Acta*, **67**, 1348 (1984).
84HCA1547 H. Hilpert and A. S. Dreiding, *Helv. Chim. Acta*, **67**, 1547 (1984).
84HCA1793 H. Wyler and A. S. Dreiding, *Helv. Chim. Acta*, **67**, 1793 (1984).
84JCS(CC)1170 M. R. Chedekel, E. J. Land, A. Thompson, and T. G. Truscott, *J. Chem. Soc., Chem. Commun.*, 1170 (1984).
84JHC1183 W. B. Lutz, C. R. McNamara, M. R. Olinger, D. F. Schmidt, D. E. Doster, and M. D. Fiedler, *J. Heterocyclic Chem.*, **21**, 1183 (1984).
84MI67 R. C. Sealy, Free radicals in melanin formation structure and reactions, in *"Free Radicals in Molecular Biology, Aging and Disease"* (D. Armstrong, R. S. Sohal, R. G. Cutler and T. F. Slater, eds.), pp. 67–76, Raven Press, New York (1984).
84TL2993 Y. Omote, A. Tomotake, and C. Kashima, *Tetrahedron Lett.*, **25**, 2993 (1984).
85BBA49 A. Thompson, E. J. Land, M. R. Chedekel, K. V. Subbarao, and T. G. Truscott, *Biochim. Biophys. Acta*, **843**, 49 (1985).
85EHP185 B. Kalyanaraman, C. C. Felix, and R. C. Sealy, *Environ. Health Persp.*, **64**, 185 (1985).
85G357 A. Napolitano, F. Chioccara, and G. Prota, *Gazz. Chim. Ital.*, **115**, 357 (1985).

85HCA1670 H. Hilpert, M. -A. Siegfried, and A. S. Dreiding, *Helv. Chim. Acta*, **68**, 1670 (1985).

85JID229 A. M. Korner and P. Gettins, *J. Invest. Dermatol.*, **85**, 229 (1985).

85JMC1273 A. K. Sinhababu, A. K. Ghosh, and R. T. Borchardt, *J. Med. Chem.*, **28**, 1273 (1985).

85JOC2790 B. P. Murphy and T. M. Schultz, *J. Org. Chem.*, **50**, 2790 (1985).

85JOC5873 B. P. Murphy, *J. Org. Chem.*, **50**, 5873 (1985).

85PTRSL679 P. A. Riley, *Phil. Trans. Roy. Soc. Lond. B*, **311**, 679 (1985).

85SC321 B. P. Murphy and H. D. Banks, *Synthetic Commun.*, **15**, 321 (1985).

85SC423 A. Meyer and B. P. Murphy, *Synthetic Commun.*, **15**, 423 (1985).

85TL2805 A. Napolitano, M. G. Corradini, and G. Prota, *Tetrahedron Lett.*, **26**, 2805 (1985).

86G407 M. d'Ischia and G. Prota, *Gazz. Chim. Ital.*, **116**, 407 (1986).

86G423 B. Pispisa, A. Palleschi, G. Paradossi, and S. Chiavarini, *Gazz. Chim. Ital.*, **116**, 423 (1986).

86HCA1588 I. Parikh, H. Hilpert, K. Hermann, and A. S. Dreiding, *Helv. Chim. Acta*, **69**, 1588 (1986).

86JCS(D)1833 R. F. Jameson and T. Kiss, *J. Chem. Soc., Dalton Trans.*, 1833 (1986).

86SC267 A. McKillop, H. M. L. Davies, and E. C. Taylor, *Synthetic Commun.*, **16**, 267 (1986).

86T2083 M. G. Corradini, A. Napolitano, and G. Prota, *Tetrahedron*, **42**, 2083 (1986).

87BBA203 A. Palumbo, M. d'Ischia, G. Misuraca, and G. Prota, *Biochim. Biophys. Acta*, **925**, 203 (1987).

87CBF123 G. Sichel, C. Corsaro, M. Scalia, S. Sciuto, and E. Geremia, *Cell Biochem. Function*, **5**, 123 (1987).

87G627 M. G. Corradini and G. Prota, *Gazz. Chim. Ital.*, **117**, 627 (1987).

87JHC941 C. B. Rogers, C. H. Blum, and B. P. Murphy, *J. Heterocyclic Chem.*, **24**, 941 (1987).

87PP229 W. H. Koch and M. R. Chedekel, *Photochem. Photobiol.*, **46**, 229 (1987).

87SC1815 F. Chioccara and E. Novellino, *Synth. Commun.*, **17**, 1815 (1987).

87T431 M. d'Ischia and G. Prota, *Tetrahedron*, **43**, 431 (1987).

87T2749 A. Napolitano, M. G. Corradini, and G. Prota, *Tetrahedron*, **43**, 2749 (1987).

87T4203 P. Palumbo, M. d'Ischia, and G. Prota, *Tetrahedron*, **18**, 4203 (1987).

87T5351 M. d'Ischia, A. Napolitano, and G. Prota, *Tetrahedron*, **43**, 5351 (1987).

87T5357 M. d'Ischia, A. Napolitano, and G. Prota, *Tetrahedron*, **43**, 5357 (1987).

87TL467 P. Palumbo, M. d'Ischia, O. Crescenzi, and G. Prota, *Tetrahedron Lett.*, **28**, 467 (1987).

87TL3775 M. I. Lim and D. G. Patil, *Tetrahedron Lett.*, **28**, 3775 (1987).

88AB335 K. Wakamatsu and S. Ito, *Anal. Biochem.*, **170**, 335 (1988).

88JCP4088 D. S. Galvão and M. J. Caldas, *J. Chem. Phys.*, **88**, 4088 (1988).

88PCR48 G. Prota, M. d'Ischia, and A. Napolitano, *Pigment Cell Res.*, **S1**, 48 (1988).

88T1803 M. G. Corradini, O. Crescenzi, and G. Prota, *Tetrahedron*, **44**, 1803 (1988).

88T6441 M. d'Ischia, A. Palumbo, and G. Prota, *Tetrahedron*, **44**, 6441 (1988).

88T7265 A. Napolitano, M. d'Ischia, and G. Prota, *Tetrahedron*, **44**, 7265 (1988).

89BBA12 C. Lambert, J. N. Chacon, M. R. Chedekel, E. J. Land, P. A. Riley, A. Thompson, and T. G. Truscott, *Biochim. Biophys. Acta*, **993**, 12 (1989).
89BBA297 A. Palumbo, M. d'Ischia, G. Misuraca, and G. Prota, *Biochim. Biophys. Acta*, **990**, 297 (1989).
89CPB3386 M. Kajiwara, K. Kurumaya, Y. Kohno, K. Tomita, and A. T. Carpenter, *Chem. Pharm. Bull.*, **37**, 3386 (1989).
89JOC5190 B. P. Murphy and T. M. Schultz, [Erratum to document cited in CA103(7):53912a], *J. Org. Chem.*, **54**, 5190 (1989).
89T6749 A. Napolitano, M. d'Ischia, G. Prota, T. Schultz, and L. J. Wolfram, *Tetrahedron*, **45**, 6749 (1989).
90BBA221 A. Palumbo, M. d'Ischia, G. Misuraca, A. Iannone, and G. Prota, *Biochim. Biophys. Acta*, **1036**, 221 (1990).
90BBA319 C. Lambert, E. J. Land, P. A. Riley, and T. G. Truscott, *Biochim. Biophys. Acta*, **1035**, 319 (1990).
90BBRC1328 J. M. Pawelek, *Biochem. Biophys. Res. Commun.*, **166**, 1328 (1990).
90JCP2630 D. S. Galvão and M. J. Caldas, *J. Chem. Phys.*, **92**, 2630 (1990).
90JCP2848 D. S. Galvão and M. J. Caldas, *J. Chem. Phys.*, **93**, 2848 (1990).
90JMC3035 S. Singh and G. Dryhurst, *J. Med. Chem.*, **33**, 3035 (1990).
90JPC6666 A. T. Al-Kazwini, P. O'Neill, G. E. Adams, R. B. Cundall, B. Jacquet, G. Lang, and A. Junino, *J. Phys. Chem.*, **94**, 6666 (1990).
90T5789 M. d'Ischia, A. Napolitano, K. Tsiakas, and G. Prota, *Tetrahedron*, **46**, 5789 (1990).
90TL6095 O. Crescenzi, C. Costantini, and G. Prota, *Tetrahedron Lett.*, **31**, 6095 (1990).
91BBA423 M. d'Ischia, A. Napolitano, and G. Prota, *Biochim. Biophys. Acta*, **1073**, 423 (1991).
91BBA1204 A. Palumbo, F. Solano, G. Misuraca, P. Aroca, J. C. Garcia-Borron, J. A. Lozano, and G. Prota, *Biochim. Biophys. Acta*, **1115**, 1204 (1991).
91BJ393 P. Aroca, F. Solano, J. C. Garcia-Borron, and J. A. Lozano, *Biochem. J.*, **277**, 393 (1991).
91JA2789 A. I. Meyers and T. M. Sielecki, *J. Am. Chem. Soc.*, **113**, 2789 (1991).
91JBC6073 M. Sugumaran and V. Semensi, *J. Biol. Chem.*, **266**, 6073 (1991).
91JCS(F)2939 C. Lambert, T. G. Truscott, E. J. Land, and P. A. Riley, *J. Chem. Soc., Faraday Trans.*, **87**, 2939 (1991).
91JCS(P2)1941 A. T. Al-Kazwini, P. O'Neill, G. E. Adams, R. B. Cundall, G. Lang, and B. Junino, *J. Chem. Soc. Perkin Trans. 2*, 1941 (1991).
91JOC1767 S. Singh and G. Dryhurst, *J. Org. Chem.*, **56**, 1767 (1991).
91MI117 K. Polewski and D. Slawinska, *Physiol. Chem. Phys. Med. NMR*, **23**, 117 (1991).
91PHA426 G. Raether, F. Lebus, D. Klopsch, D. Katzorke, and H. Wollmann, *Pharmazie*, **46**, 426 (1991).
91TL3849 C. Costantini, O. Crescenzi, and G. Prota, *Tetrahedron Lett.*, **32**, 3849 (1991).
92EJ519 K. Tsukamoto, I. J. Jackson, K. Urabe, P. M. Montague, and V. J. Hearing, *EMBO J.*, **11**, 519 (1992).
92FEBS126 A. K. Chakraborty, S. J. Orlow, and J. M. Pawelek, *FEBS Lett.*, **302**, 126 (1992).
92JA8483 A. I. Meyers, T. M. Sielecki, D. C. Crans, R. W. Marshman, and T. H. Nguyen, *J. Am. Chem. Soc.*, **114**, 8483 (1992).
92MI2 G. Prota, Melanins and Melanogenesis, Academic Press, San Diego, CA (1992).

92TL3045 A. T. Al-Kazwini, P. O'Neill, R. B. Cundall, G. E. Adams, A. Junino, and J. Maignan, *Tetrahedron Lett.*, **33**, 3045 (1992).

93BBA175 A. Napolitano, A. Palumbo, G. Misuraca, and G. Prota, *Biochim. Biophys. Acta*, **1168**, 175 (1993).

93BC392 F. Zhang and G. Dryhurst, *Bioorg. Chem.*, **21**, 392 (1993).

93JCS(F)803 E. J. Land, *J. Chem. Soc., Faraday Trans.*, **89**, 803 (1993).

93JCS(P2)2435 W. Linert, E. Herlinger, and R. F. Jameson, *J. Chem. Soc., Perkin Trans. 2*, 2435 (1993).

93JOC1607 J. F. Carpenter, *J. Org. Chem.*, **58**, 1607 (1993).

93PHA273 H. Baran and G. Schwedt, *Pharmazie*, **48**, 273 (1993).

93T9143 A. Napolitano, O. Crescenzi, K. Tsiakas, and G. Prota, *Tetrahedron*, **49**, 9143 (1993).

93TL885 A. Napolitano, O. Crescenzi, and G. Prota, *Tetrahedron Lett.*, **34**, 885 (1993).

94BBA53 C. Salinas, J. C. Garcia-Borron, F. Solano, and J. A. Lozano, *Biochim. Biophys. Acta*, **1204**, 53 (1994).

94BJ839 A. Palumbo, M. d'Ischia, G. Misuraca, L. De Martino, and G. Prota, *Biochem. J.*, **299**, 839 (1994).

94JMC1084 F. Zhang and G. Dryhurst, *J. Med. Chem.*, **37**, 1084 (1994).

94JVST(B)1512 G. W. Zajac, J. M. Gallas, and A. E. Alvarado-Swaisgood, *J. Vac. Sci. Technol., B*, **12**, 1512 (1994).

94MR343 A. T. Al-Kazwini, P. O'Neill, G. E. Adams, R. B. Cundall, J. Maignan, and B. Junino, *Melanoma Res.*, **4**, 343 (1994).

94PCR263 J. Cheng, S. C. Moss, and M. Eisner, *Pigment Cell Res.*, **7**, 263 (1994).

95JCS(P2)259 E. Herlinger, R. F. Jameson, and W. Linert, *J. Chem. Soc., Perkin Trans. 2: Phys. Org. Chem.*, 259 (1995).

95JMC917 A. Napolitano, O. Crescenzi, A. Pezzella, and G. Prota, *J. Med. Chem.*, **38**, 917 (1995).

95MI94 G. Prota, *Fortschr. Chem. Org. Naturst.*, **64**, 94 (1995).

95PP650 S. Schmitz, P. D. Thomas, T. M. Allen, M. J. Poznansky, and K. Jimbow, *Photochem. Photobiol.*, **61**, 650 (1995).

96G783 M. d'Ischia, A. Napolitano, and G. Prota, *Gazz. Chim. Ital.*, **126**, 783 (1996).

96JCS(P2)241 A. T. Al-Kazwini, P. O'Neill, G. E. Adams, R. B. Cundall, J. Maignan, and A. Junino, *J. Chem. Soc., Perkin Trans. 2*, 241 (1996).

96JMC5192 A. Napolitano, A. Palumbo, M. d'Ischia, and G. Prota, *J. Med. Chem.*, **39**, 5192 (1996).

96NPL137 K. T. Wong, B. K. H. Tan, K. Y. Sim, and S. H. Goh, *Nat. Prod. Lett.*, **9**, 137 (1996).

96T7913 A. Pezzella, A. Napolitano, M. d'Ischia, and G. Prota, *Tetrahedron*, **52**, 7913 (1996).

96TL4241 A. Napolitano, A. Pezzella, M. d'Ischia, and G. Prota, *Tetrahedron Lett.*, **37**, 4241 (1996).

97B408 P. A. Riley, *Biologist*, **44**, 408 (1997).

97BBA61 S. Memoli, A. Napolitano, M. d'Ischia, G. Misuraca, A. Palumbo, and G. Prota, *Biochim. Biophys. Acta*, **1346**, 61 (1997).

97BJ25 S. Baez, J. Segura-Aguilar, M. Widersten, A. S. Johansson, and B. Mannervik, *Biochem. J.*, **324**, 25 (1997).

97JBC5727 J. Segura-Aguilar, S. Baez, M. Widersten, C. Welch, and B. Mannervik, *J. Biol. Chem.*, **272**, 5727 (1997).

97JBC26226 C. J. Cooksey, P. J. Garratt, E. J. Land, S. Pavel, C. A. Ramsden, P. A. Riley, and N. P. M. Smit, *J. Biol. Chem.*, **272**, 26226 (1997).

97JCS(D)2813 U. El-Ayaan, E. Herlinger, R. F. Jameson, and W. Linert, *J. Chem. Soc., Dalton Trans.*, 2813 (1997).
97JMC2211 A. Pezzella, M. d'Ischia, A. Napolitano, G. Misuraca, and G. Prota, *J. Med. Chem.*, **40**, 2211 (1997).
97MR478 A. Palumbo, U. Mars, L. De Martino, M. d'Ischia, A. Napolitano, B. S. Larsson, and G. Prota, *Melanoma Res.*, **7**, 478 (1997).
97MR517 E. Rosengren, S. Thelin, P. Aman, C. Hansson, L. Jacobsson, and H. Rorsman, *Melanoma Res.*, **7**, 517 (1997).
97T8281 A. Pezzella, M. d'Ischia, A. Napolitano, A. Palumbo, and G. Prota, *Tetrahedron*, **53**, 8281 (1997).
98BBA27 L. Novellino, M. d'Ischia, and G. Prota, *Biochim. Biophys. Acta*, **1425**, 27 (1998).
98CNC512 É. N. Novruzov, *Chem. Nat. Compounds*, **34**, 512 (1998).
98JCS(CC)77 J. Clews, C. J. Cooksey, P. J. Garratt, E. J. Land, C. A. Ramsden, and P. A. Riley, *J. Chem. Soc., Chem. Commun.*, 77 (1998).
98JCS(D)1315 U. El-Ayaan, R. F. Jameson, and W. Linert, *J. Chem. Soc., Dalton Trans.*, 1315 (1998).
98JOC7002 P. Manini, M. d'Ischia, M. Milosa, and G. Prota, *J. Org. Chem.*, **63**, 7002 (1998).
98MI307 G. Prota, M. d'Ischia, and A. Napolitano, in *"The Pigmentary System: Its Physiology and Pathophysiology"* (J. J. Nordlund, R. E. Boissy, V. J. Hearing, R. A. King and J. P. Ortonne, eds.), p. 307, Oxford University Press, New York (1998) Chapter 24.
98P1593 W. Schliemann, U. Steiner, and D. Strack, *Phytochemistry*, **49**, 1593 (1998).
99CMB1035 J. Matsunaga, D. Sinha, F. Solano, C. Santis, G. Wistow, and V. Hearing, *Cell Mol. Biol. (Noisy-le-Grand)*, **45**, 1035 (1999).
99CRT985 L. Novellino, A. Napolitano, and G. Prota, *Chem. Res. Toxicol.*, **12**, 985 (1999).
99JES256 H. J. Zhang, X. Wu, W. Zhang, and S. Chen, *J. Electrochem. Soc.*, **146**, 256 (1999).
99JPC(B)2993 L. E. Bolívar-Marinez, D. S. Galvão, and M. J. Caldas, *J. Phys. Chem., B*, **103**, 2993 (1999).
99SYN793 L. Novellino, M. d'Ischia, and G. Prota, *Synthesis*, 793 (1999).
00JCS(P1)4306 J. Clews, C. J. Cooksey, P. J. Garratt, E. J. Land, C. A. Ramsden, and P. A. Riley, *J. Chem. Soc., Perkin Trans. 1*, 4306 (2000).
01JA9606 K. -Q. Ling, J. Kim, and L. M. Sayre, *J. Am. Chem. Soc.*, **123**, 9606 (2001).
01JPP(B)123 E. J. Land, C. A. Ramsden, and P. A. Riley, *J. Photochem. Photobiol., (B)*, **64**, 123 (2001).
01MI2466 F. Lemos-Amado, P. Domingues, A. Ferrer-Correia, F. Remiao, N. Milhazes, F. Borges, F. D. Carvalho, and M. L. Bastos, *Rapid Commun. Mass Spectr.*, 2466 (2001).
01NR157 J. Segura-Aguilar, D. Metodiewa, and S. Baez, *Neurotoxicity Res.*, **3**, 157 (2001).
01ZN714 T. Kujala, K. Klika, V. Ovcharenko, J. Loponen, M. Vienola, and K. Pihlaja, *Z. Naturforsch.*, **56c**, 714 (2001).
02AC5047 G. J. Van Berkel, K. G. Asano, and V. Kertesz, *Anal. Chem.*, **74**, 5047 (2002).
02BJ333 Q. Han, J. Fang, H. Ding, J. K. Johnson, B. M. Christensen, and J. Li, *Biochem. J.*, **368**, 333 (2002).
02JOC6671 K. M. Meragelman, L. M. West, P. T. Northcote, L. K. Pannell, T. C. McKee, and M. R. Boyd, *J. Org. Chem.*, **67**, 6671 (2002).
02T3681 A. Pezzella, D. Vogna, and G. Prota, *Tetrahedron*, **58**, 3681 (2002).

03ACR300	E. J. Land, C. A. Ramsden, and P. A. Riley, *Acc. Chem. Res.*, **36**, 300 (2003).
03CPL532	K. Bochenek and E. Gudowska-Nowak, *Chem. Phys. Lett.*, **373**, 532 (2003).
03JPC(B)3061	K. B. Stark, J. M. Gallas, G. W. Zajac, M. Eisner, and J. T. Golab, *J. Phys. Chem., B*, **107**, 3061 (2003).
03JPC(B)7162	Y. V. Il'ichev and J. D. Simon, *J. Phys. Chem. B*, **107**, 7162 (2003).
03JPC(B)11558	K. B. Stark, J. M. Gallas, G. W. Zajac, M. Eisner, and J. T. Golab, *J. Phys. Chem., B*, **107**, 11558 (2003).
03MI1689	J. Di and S. Bi, *Acta A*, **59**, 1689 (2003).
03MI3075	J. Di and S. Bi, *Spectrochim. Acta A*, **59**, 3075 (2003).
03OBC3120	E. J. Land, C. A. Ramsden, P. A. Riley, and G. Yoganathan, *Org. Biomol. Chem.*, **1**, 3120 (2003).
03PCR397	E. J. Land, C. A. Ramsden, P. A. Riley, and G. Yoganathan, *Pigment Cell. Res.*, **16**, 397 (2003).
03PCR487	E. J. Land, S. Ito, K. Wakamatsu, and P. A. Riley, *Pigment Cell. Res.*, **16**, 487 (2003).
03SL1853	S. Atkinson and P. Meredith, *Synlett.*, **12**, 1853 (2003).
03TA1133	A. Pezzella, D. Vogna, and G. Prota, *Tetrahedron Asymm.*, **14**, 1133 (2003).
04JCP8608	B. J. Powell, T. Baruah, N. Bernstein, K. Brake, R. H. McKenzie, P. Meredith, and M. R. Pederson, *J. Chem. Phys.*, **120**, 8608 (2004).
04MI1	E. J. Land, C. A. Ramsden, and P. A. Riley, *Methods Enzymol*, **378A**, 88 (2004).
04MI67	M. Sechi, G. Angotzi, R. Dallocchio, A. Dessi, F. Carta, L. Sannia, A. Mariani, S. Fiori, T. Sanchez, L. Movsessian, C. Plasencia, and N. Neamati, *Antiviral Chem. Chemotherapy*, **15**, 67 (2004).
04ND468	C. Arriagada, I. Paris, M. J. Sanchez de las Matas, P. Martinez-Alvarado, S. Cardenas, P. Castaneda, R. Graumann, C. Perez-Pastene, C. Olea-Azar, E. Couve, M. T. Herrero, P. Caviedes, and J. Segura-Aguilar, *J. Neurobiol Dis.*, **16**, 468 (2004).
04T60	S. P. H. Mee, V. Lee, J. E. Baldwin, and A. Cowley, *Tetrahedron*, **60**, 3695 (2004).
05MI3	E. J. Land, C. A. Ramsden, and R. A. Riley, Toxicological Aspects of Melanin and Melanogenesis, in "*The Pigmentary System: Physiology & Pathophysiology*" 2nd edn., (R. Boissy, R. A. King, J. Nordlund, V. J. Hearing, J.-P. Ortonne, eds.), Blackwell Publishers, Oxford, in press.

Syntheses, Structures and Interactions of Heterocalixarenes

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I. Introduction

Molecular recognition involving multimolecular entities formed between chemical species of complementary topology through non-covalent interactions is a phenomenon at the core of biology and chemistry (95MI1). To understand complex modes of recognition of biological receptors, investigations on structurally simpler models of synthetic receptors are an area of contemporary research activity. Starting with

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crown ethers – the first-generation synthetic receptors, followed by their second generation – cyclodextrins, the third generation is constituted by calix[*n*]arenes (97CRV1713). These are a category of *m*-cyclophanes, e.g., **1** (calix[4]arene, $n = 1$), elaborating a cyclic array of aromatic phenolic rings joined at 1,3-positions by methylene bridges and which when appropriately modified structurally, exhibit versatile binding character (98MI1). Structural uniqueness, responsible for their molecular recognition status, is characterized by (i) a core of aromatic rings (π-electron-rich cavity) providing π-cation, $\pi-\pi$, –CH…π, etc. interactions, (ii) derivatization at rims generating varied possibilities of receptor designs capable of crown-type bindings and (iii) tunability of a cavity in respect to its size ($n = 4, 5, 6, \ldots$), depth, and conformation such as a cone, partial cone, and 1,2-/1,3-alternate geometry (Figure 1).

The replacement of phenolic unit(s) of calix[*n*]arenes **1** by heterocyclic ring(s) and methylene bridge(s) by heteroatom(s) constitute chemical entities now, respectively, designated as heterocalixarenes (e.g., **2** calix[4]pyrrole) and heteracalixarenes (e.g., **3** thiacalix[4]arene) (99ACR729). Depending on the nature of the heterocyclic ring(s), heterocalixarenes can have both electron-rich (pyrrole) as well as electron-deficient (pyridine) π-electron character of the cavity. The substitution and ring-transformation profiles of constituent sub-heterocycles can assist in tuning the physicochemical character of heterocalixarenes. Heteroatoms can also influence their binding character. With these additional features, heterocalixarenes should be capable of providing a wider range of rational designs of synthetic receptors and consequent recognition events than calixarenes. This chapter is aimed at presenting an all comprehensive review on the synthesis, structures, chemical ring transformations and interactions of heterocalixarenes except calix[*n*]pyrroles, which constitute the subject of many recent reviews (2000MI1, 2001CCR57, 98JCS(CC)1). Heterocalixarenes possessing heteroatom(s) bridge(s) are incorporated along with the parent systems. Depending on the nature of the heterocyclic ring, the heterocalixarenes are classified into different categories. Hybrid heterocalixarenes possessing combinations of heterocycles are discussed along with the systems in which one of the heterocyclic constituents of the hybrid appears first. The sizes of heterocalixarenes and linear oligomers are denoted by C_n and L_n and the

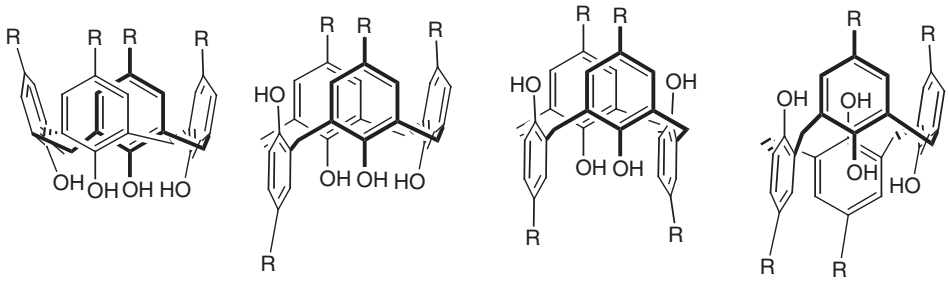
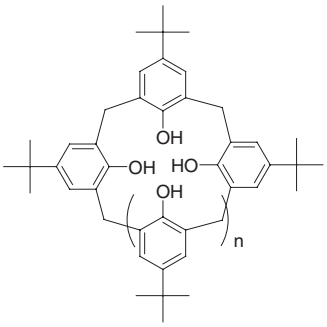
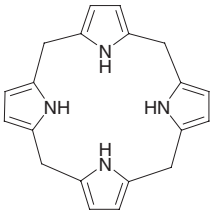


Figure 1

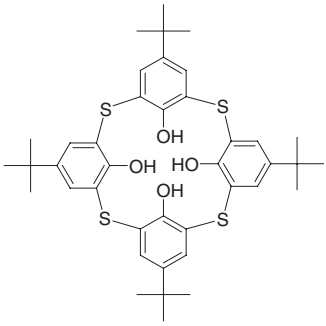
nomenclature of the heterocalixarenes takes cognisance of the nature and number of *meta*-linked nuclei.



(1)



(2)



(3)

For simplicity in presentation, the following nomenclature to describe the composition of materials with repeating units is used. Thus, C_4 serves as shorthand to designate a substance with four repeating units as in **4**. The substituents present on methylene bridges are prefixed to describe substituted calixarene. Hence, octamethylcalix[4]furan **4** represents a heterocalixarene with four repeating furan units and two methyl units each on four methylene bridges. Moreover, the structures such as **9** are generalized and indicate the number of repeating *n*-units. Thus, L_3 **9** denotes a linear oligomer (L) with $n = 3$ repeating units.

II. Calix[*n*]furans and their Hybrid Systems

A. General

As oxygen analogues of calix[*n*] pyrroles, the mother nucleus of biochemically so significant porphyrins, calix[*n*]furans constitute a cavity having a π-electron-rich nature of the calixarene molecular frame and a hydrophilic character of crown ethers with the difference that the furan O-atom has less donating ability than an ether oxygen. Furans have a proven capability to undergo facile chemical transformations of synthetic significance (74MI1). Thus in addition to their inbuilt receptor capability, a molecular scaffold of calix[*n*]furans elaborates a unique scope of generating many otherwise inaccessible chemical entities including artificial receptors.

B. Syntheses and Structures

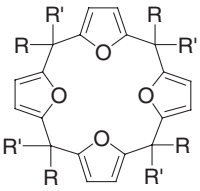
1. *Single-Step Syntheses*

A direct, straightforward synthesis involves acid-catalysed reactions of carbonyl compounds and furan. Ackman et al. optimized the use of furan and acetone in 1:2 ratio and evolved the first ever synthesis of octamethylcalix[4]furan (**4**) (55JOC1147).

The initially controversial template effect of $LiClO_4$ (73JCS(CC)534) and $LiClO_4(DME)_2$ (77OS74) and the beneficial role of lithium perchlorate in enhancing the yield of **4** was subsequently rationalized as due to a pH effect (81JCS(CC)149, 85JCS(P1)973). The use of $LiClO_4 \cdot (DME)_2$ has been discouraged and through an ^{1}H-NMR-based analysis of the reaction products of $LiClO_4$ catalysed reaction of furan and acetone (1:6), it has been found that the corresponding C_4, C_5 and C_6 products are formed in the ratio 12.5:1:1.5 (96TL4593). Substituted methyl ketones, cyclohexanone, aliphatic ketoacids/esters and aldehydes all react with furan in the presence of acid to form linear oligomers and in no case is any cyclic calix[*n*]furan isolated (56CJC1147, 56JOC447, 58CJC537, 71CJC4017, 76JA7414, 91JHC991). Benzaldehyde and furfural fail to react with furan. On using $LiClO_4$ as catalyst, methyl alkanones as well as cyclohexanone react with furan in presence of HCl to form the corresponding calix[4]furans in improved yields (85JCS(P1)973).

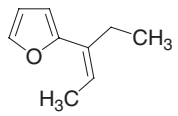
In another version of the single-step approach, $ZnCl_2$/HCl catalysed cyclocondensation of commercially available furfuryl alcohol uniquely provides the parent calix[4]furan (**7**) in 1% yield and the method on comparison with subsequently reported other methods has been advocated as a convenient preparative scale approach (89AGE1651).

The revision of the originally assigned structure 3-furyl-2-pentene (**8**) to the product of acid-induced dehydration of 3-furyl-3-pentanol to C_4 **6** virtually constitutes an unrecognized first synthesis of any heterocalixarene (06MI1, 55JOC1147). Despite the availability of starting ethyl furoate used in obtaining such furfuryl alcohols through Grignard reactions and consequent inbuilt possibility of embroidering methylene bridges of calix[4]furan, this method has not so far been adequately investigated.



(**4** - **7**)

(**4**) R, R' = Me
(**5**) R = Me, R' = Et
(**6**) R, R' = Et
(**7**) R, R' = H



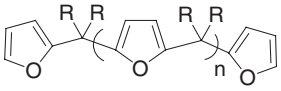
(**8**)

2. *Two-Step Syntheses*

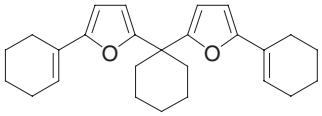
An indirect two-step synthetic methodology for calix[*n*]furans (C_n) involves the formation of linear oligomers (L_n) from furan and carbonyl compounds, followed by condensations of various L_n and carbonyl compounds or cyclization of an appropriate linear oligomer with a carbonyl compound. On the whole, this methodology constitutes a directed approach for a specified target but its utility depends largely on the availability of the precursor linear oligomers.

a. Linear Oligomers (L_n). Acid-catalysed reactions of furan and ketones in 1:1 or 2:1 stoichiometry usually form mixtures of linear oligomers L_2 **9**, L_3 **9** and L_4 **9**,

which can be isolated by fractional distillation (56CJC537, 56JOC447, 55JOC1147). In the case of the reaction of formaldehyde and furan, formation of a corresponding L_2 (56CJC1147) and a mixture of L_2, L_3 and L_4 (91JHC991) are reported. BF_3 catalysed reaction of furan and furfuryl alcohol forms mainly L_2 but the corresponding L_3 and L_7 are also isolated in low yields (94JCS(P1)2881). Higher aldehydes and ketoesters form the corresponding L_2 (56CJC1147). Cyclohexanone and furan (1:2) form as usual L_2 and L_3 but when taken in stoichiometric ratio 2:1, **10** is formed (71CJC4017).



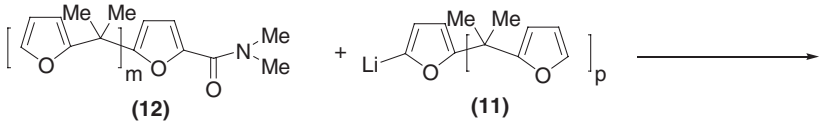
(9)



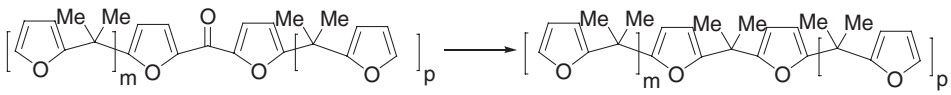
(10)

A practical and compendious general route, directed towards both odd- and even-membered linear oligomers upto L_8, has been recently discovered by Rees et al. (2001JCS(P1)3297). It involves the use of L_2 and L_3 formed from furan and acetone (2:1) and basically the reactions of their metalated furan units **11** with an appropriate electrophilic carbamoyl derivative **12** of the furan ring to link furans and form ketones **13** which are converted to **14** employing Me_2 Zn–Ti Cl_4.

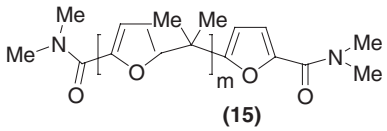
The reactions of appropriate combinations of monometalated L_2 or L_3 **11** with ethoxycarbonylmorpholine or *N*-formylmorpholine or morpholine analogue of L_2 **12** form symmetrical and unsymmetrical monoketones that are converted to the corresponding L_3 to L_6 **14** having isopropyl linkers. A similar sequence of reactions of monometalated furan or L_2 or L_3 **11** with L_2 or L_3 **15** ultimately yield the diketones which provide L_4 to L_8 **14** of which L_7 and L_8 were obtained for the first time. Lastly, combinations of dimetalated L_2 or L_3 **16** and *N*-furoylmorpholine or L_2 **12** have been used for procuring the corresponding diketones, the precursors of L_4 to L_7. The largest diketone **17** was formed from dimetalated L_3 **16** and L_3 **12** or more effectively from L_3 **15** and L_3 **11** (2001JCS(P1)3297). Di- or trimeric linear oligomers obtained from furan and acetone and acetaldehyde individually, as well as these mixed oligomers have been condensed with carbonyl compounds to form L_4 to L_6 **14** having the same or mixed linkers (76JA7414).



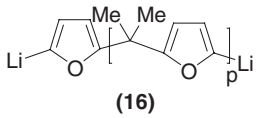
(12) **(11)**



(13) **(14)**



(15)



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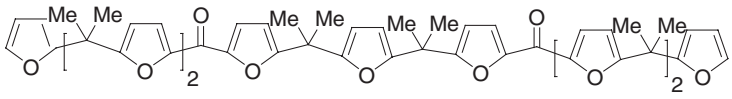
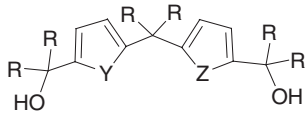


(17)

Hybrid linear tri- and tetra-oligomers possessing combinations of furan, thiophene or pyrrole have been obtained (2000TL2919, 2001T7323) by BF_3-catalysed reactions of diols **18**, and **22** with pyrrole, etc. The diols are obtained from reactions of bisanions of the parent heterocycles or their dimers with ketones.

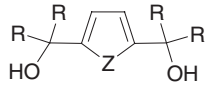


(**18**) Y, Z = O, R = Me

(**19**) Y, Z = O, R = Et

(**20**) Y, Z = S, R = Et

(**21**) Y = S, Z = O, R = Me

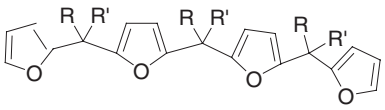


(**22**) Z = O
(**23**) Z = S

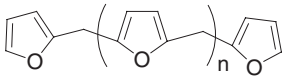
b. Cyclocondensations of Linear Oligomers. A direct single-step approach, frequently plagued by the formation of mixtures of C_n, is by and large limited to the formation of even-membered heterocalixarenes and the synthesis of larger-sized systems is hampered by the fact that C_4 constitutes a sink for the growing oligomer chain. In comparison, L_n of the size of C_n on reaction with a carbonyl compound forms only the target C_n. The condensation of combinations of the same or different L_n with ketones also generates mainly the target C_n. This methodology has been used in procuring C_4 to C_9.

Again, Ackman and co-workers (56JOC1147) pioneered the use of this approach by cyclizing L_4 **9** (R = Me) with butan-2-one and pentan-2-one to form the corresponding calix[*n*]furans with new bridge substituents, Me, Et and Et, Et in good yields. The same L_4 was also cyclized with cyclohexanone (71CJC4017, 2004S865), chloroacetone, ethyl acetoacetate, levulinic acid and pyruvic acid (58CJC537) to form calix[*n*]furans having varied substituents at one of the linkers in very good yields. Acid-catalysed cyclizations of L_4, **24** (R = Me, R′ = Et) with butan-2-one

(58CJC537) and **24** (R, R′ = Et) with pentan-3-one (56JOC447) formed **5** and **6**, respectively. Linear tetramers **24** (R = Me, R′ = H or Me) on reaction with acetaldehyde, acetone and ethyl levulinate gave the corresponding C_4 having new bridge substituents, Me, H ; Me, Me and Me, -CH_2CH_2COOEt (76JA7414).



(**24**)



(**25**)

Octaethylcalix[4]furan (**6**) in its X-ray structure (94JA10775) showed a double saddle-shaped conformation with two cavities where both C ═C and C–H bonds are exposed and accessible to appropriate metal ion for interaction. The octamethylcalix[4]furan (**5**), in its X-ray structure reveals a square ring conformation with furan rings alternately up and down (89AX(C)137).

Cyclization of linear oligomers L_n having –CH_2– linkers in contrast with those having substituents, undergo decomposition in the presence of HCl. Therefore, L_4 **25** on reaction with HCHO–HCl, even in the presence of LiCl gives a resinous mass (91JHC991). However, in a versatile $BF_3 \cdot Et_2O$ catalysed reaction using $CH_2(OMe)_2$, L_4 **25** cyclized to C_4 **7** (94JCS(P1)2881). Likewise in a (2 + 2) cyclization of difurylmethane L_2 **25** with $CH_2(OMe)_2$ in the presence of $BF_3 \cdot Et_2O$, **7** was formed in 6% yield whereas HCHO failed to react. But Vogel (88AGE409) reported 0.5–1% yield of **7** from difurylmethane and HCHO in the presence of $LiClO_4$. Acid-catalysed condensation of 5,5-methylene-di-2-furaldehyde and difurylmethane followed by oxidation with nitric acid and treatment with $HClO_4$ gives dication **26** (88AGE406), which is also formed by oxidation of calix[4]furan (**7**) (89AGE1651).

Calix[4]furan (**7**) crystallized from ethanol in monoclinic and triclinic forms. Their X-ray structures (88AGE409) reveal that **7** exists in single conformation (Figure 2a) in monoclinic form and in two different conformations (Figures 2b and c) in triclinic form. The molecules in monoclinic form have approximately D_{2d} symmetry and the two molecular structures of triclinic form have two related conformations, one of which is characterized by a centre of symmetry. The dication **26** in its X-ray structure (88AGE406) is nearly planar and its molecular shape is largely in agreement with that of porphyrin. The two perchlorate ions are situated above and below the ring framework.

Various L_2 **9** formed from furan and ketones including cyclohexanone, on acid-catalysed condensation with a relevant ketone, provide calix[4] furans having the same or varied bridge substituents in good yields. (55JOC1147, 56JOC447, 58CJC537, 71CJC4017, 2004S865). L_2 **9** and **10** react to form calix[4]furan having spiro cyclohexylidene bridges (71CJC4017), alternatively obtained from furan and cyclohexanone in the presence of Li^+. Kohnke and co-workers (96TL4593) confirmed Ackman's observation (55JOC1147) that the use of an excess of acetone over

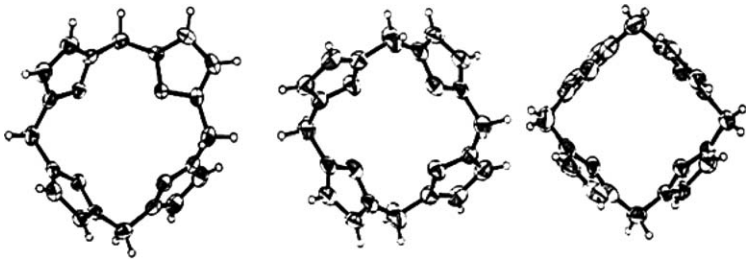
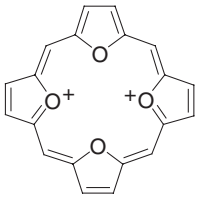
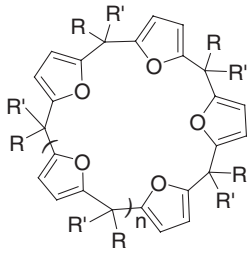


Figure 2. X-ray structure of **7** (a) monoclinic form; (b) and (c) triclinic form. (Reprinted with permission from 88AGE409, Copyright 1988, John Wiley & Sons Inc.)

furan always favours C_4 formation and it was also noticed that condensations of equimolar amounts of acetone with L_2 **9** and L_3 **9** form a mixture of the corresponding C_4, C_5 and C_6 with predominant C_4 and least favoured C_5.



(**26**)



(**27** - **32**)

(**27**) n = 1; R, R' = H
(**28**) n = 1; R, R' = Me
(**29**) n = 2; R, R' = Me
(**30**) n = 2; R, R' = H
(**31**) n = 4; R, R' = H
(**32**) n = 5; R, R' = Me

$BF_3 \cdot Et_2O$ induced cyclization of L_5 **25** with $CH_2(OMe)_2$ gave **27** in 5% yield (94JCS(P1)2881). The formation of decamethylcalix[5]furan (**28**) is disfavoured in a direct condensation method as well as in a condensation of appropriate L_2 and L_3 (96TL4593, 91CB233). HCl gas induced condensation of L_5 **9** (R = Me) with acetone forms **28** in 45% yield (76JA7414) but yields drop over longer reaction time (2001JCS(P1)3297).

Acid-catalysed reaction of L_3 **9** (R = Me) with acetone formed dodecamethylcalix[6]furan (**29**) (55JOC1147) along with linear oligomers L_9, L_{12}, L_{15} and L_{18}. Using a dilution technique and slow addition of reactants to EtOH/HCl, Kohnke et al. obtained **29** (96TL4593) and traces of the corresponding C_9 were detected by EIMS. This preparation has now been further improved and no longer requires the use of chromatography. The reaction mixture is extracted with hot ethyl acetate and the product crystallizes from the extract on cooling (2000AGE1496). HCl gas (76JA7414) and conc. HCl, $LiClO_4$ or $CsClO_4$ (85JCS(P1)973) induced reactions of L_6 **9** (R = Me) with acetone gave C_6 **29** in over 50% yield. The parent calix[6]furan (**30**) with unsubstituted methylene bridges was obtained in 1% yield from L_6 **25** by a $BF_3 \cdot Et_2O$ catalysed reaction with $CH_2(OMe)_2$ (94JCS(P1)2881).

Dodecamethylcalix[6]furan (**29**) in its X-ray structure (96TL4593) shows C_2 symmetry about an axis passing through two of the furan rings those containing O(1) and O(24) (Figure 3). The macrocycle is self-filling, four of the furan rings being oriented approximately orthogonally with respect to the mean plane of the macrocycle whereas the other two lie almost within the plane. There is no significant intra or intermolecular close contact to any of the six furan O atoms and there is no CH…π interaction.

Calix[7]furan derivatives are unknown. However, a recent practical synthesis of L_7 **9** (R = Me) (2001JCS(P1)3297) may pave the way for its synthesis. Earlier, in the $BF_3 \cdot Et_2O$ catalysed condensation of furyl alcohol and furan (1:2), the formation of L_7 **25** was reported in 0.5% yield (94JCS(P1)2881).

The parent calix[8]furan was formed in traces in a $BF_3 \cdot Et_2O$ induced reaction of L_3 **25**, difuryl methane and $CH_2(OMe)_2$ (94JCS(P1)2881). HCl induced cyclization of L_4 **9** (R = Me) with acetone gave C_8 **31** in low yield along with major product C_4 **4** (85JCS(P1)973). The availability of L_8 **9** (R = Me) (2001JCS(P1)3297) now could facilitate its formation.

Acid-induced macrocyclization of L_3 **9** (R = Me) and acetone did not form the corresponding calix[9]furan either due to the insolubility of L_9 or due to the unfavoured macrocyclization. However, L_9 (R = Me) when solubilized on treatment with 6 mol of acetone in benzene saturated with HCl readily cyclized to C_9 **32** in 45% yield. When L_3 **9** was subjected to macrocyclization under these conditions, the isolated yields of C_6 **29** and C_9 **32** were 18% and 6.5%, respectively (96TL4593).

To provide additional coordination sites, silicon bridged calix[4]furan **33** ($n = 1$) and calix[6]furan **33** ($n = 3$) were formed by a condensation of lithiated furan with Me_2SiCl_2 in 16% and 10% yields, respectively. The X-ray crystal structure of **33** ($n = 1$) shows a 1,3-alternate conformation of the macrocycle (95JOC7406).

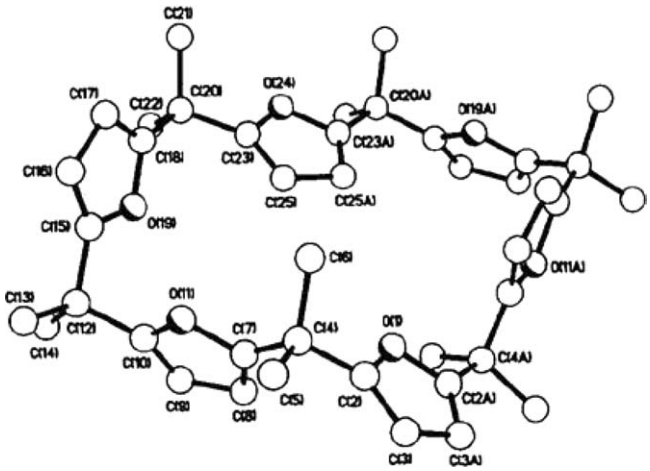
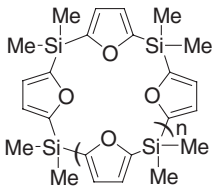
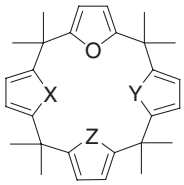


Figure 3. The X-ray crystal structure of dodecamethylcalix[6]furan (**29**). (Reprinted with permission from 96TL4593, Copyright 1996, Elsevier.)



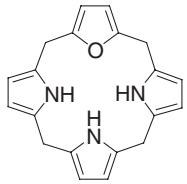
(**33**)



(**34**) X,Y = O; Z = NH

(**35**) X = O; Y,Z = NH

(**36**) X,Y = NH; Z = O



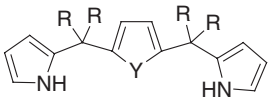
(**37**)

Like the core size, the variation of core sub-heterocycles in heterocalixarenes evolving customized hybrid heterocalixarenes containing varied combinations of furan, pyrrole and thiophene could result in tuning the binding character of heterocalixarenes. The first synthesis (58CJC371) of such systems having furan and pyrrole in stoichiometeric ratios 3:1 **34**, and 2:2 **35**, involving acid-catalysed condensation of 2,2-*bis*(5-isopropylolfuryl)propane (**18**) with 2-furyl-2-pyrrylpropane and 2,2-dipyrrylpropane, respectively dates back to 1958. Calix[2] furan[2]pyrrole **36**, having an alternate array of furan and pyrrole rings that could be ideal for non-bonding interactions with guest molecules, was obtained by acid-catalysed condensation of **22** (R = Me) with pyrrole and 2-furyl-2-pyrrylpropane with acetone (58CJC371) as well as by homologation of calix[4]furan detailed in Section II.C. The X-ray structure of **36** indicates its C_2 symmetry and 1,3-alternate conformation (2000TL2919). The reactions of diols **19**–**21** with 2,2-dipyrrylmethane in the presence of BF_3 form the corresponding hybrid calix[2]furan[2]pyrrole, calix[2]thiophene[2]pyrrole and calix[1]thiophene[1]furan[2]-pyrrole derivatives (2004TL299). A similar approach has been used to procure a calix[2]thiazole[2]pyrrole system also.

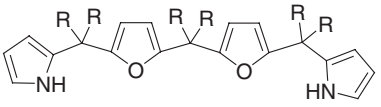
In $BF_3 \cdot Et_2O$-catalysed (3 + 1) condensations of **38** (Y = NH, R = H) and **38** (Y = O, R = H) with 2,5-*bis*(hydroxymethyl)pyrrole, unsubstituted calix[4]pyrrole (**2**) and calix[1]furan[3]pyrrole (**37**), respectively, were isolated for the first time (2001T2103). The appearance of only two singlets for four methylene bridges in the ^{1}H NMR spectrum of **37** suggests its conformational inversion in solution. However, its X-ray structure reveals 1,2-alternate conformation in the solid state.

Lee and co-workers (2000OL3115, 2000TL2919, 2001T7323) synthesized a host of hybrid heterocalixarenes, C_n (n = 4, 5, 6, 8, 10, 12, 15) containing various combinations of furan, pyrrole and thiophene as well as bridge substituents using $BF_3 \cdot Et_2O$-catalysed condensations of appropriate linear oligomers in (3 + 1), (3 + 2), (3 + ketone) and (4 + 2) approaches. Condensation of **22** (R = Me) and **23** (R = Me) with **38** (Y = O or S, R = Me) formed mixtures of C_4 **40**, C_6 **41** and C_8 **42** with Z, Y = O or S and Z = O, Y = S where C_4 was the major component. The formation of C_6 with an alternating furan and pyrrole arrangement points to the acid-catalysed reversible cleavage of starting material during this reaction. The X-ray structure of C_6, **41** (Z, Y = O) (2000AGE1496) crystallized from ethanol, is similar to that of calix[6]pyrrole but crystals are free from included solvent. It has a tennis-ball

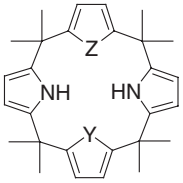
geometry and this conformation which is self-filling is in part stabilized by an intramolecular NH…O hydrogen bond between the N_4 pyrrole and the O_3 furan ring atom. Surprisingly, there is no other H-bonding interaction.



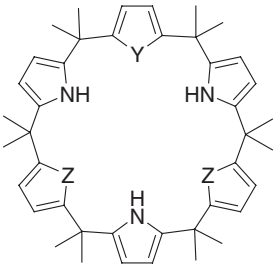
(**38**)



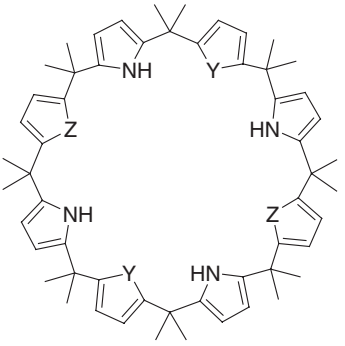
(**39**)



(**40**)

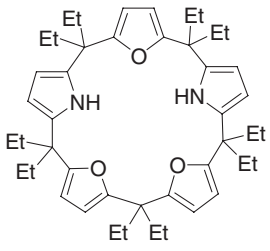


(**41**)

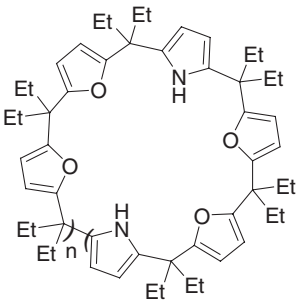


(**42**)

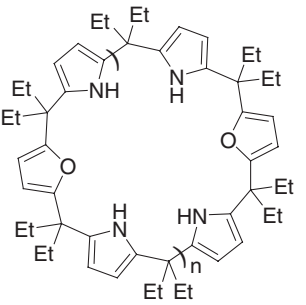
In a (3 + 2) condensation of **38** (Y = O, R = Et) and **19**, the corresponding C_5 **43** (55%) and C_{10} (15%) were formed. Cyclic hexamer **44** and dodecamer **45** were procured in a (4 + 2) condensation of **39** and **19**. Linear trimer **38** (R = Et, Y = O) was condensed with acetone to form a mixture of **46** ($n = 1-4$, R = Me) including a super-expanded pentadecameric system (2000OL3115, 2001T7323). **43** in the solid state adapts a bowl-shaped modified alternating conformation wherein two adjacent furans are coplanar and point inwards (2002TL9493). All these reactions could be applied to thiophene containing analogues.



(**43**)



(**44**) n = 1
(**45**) n = 2



(**46**)

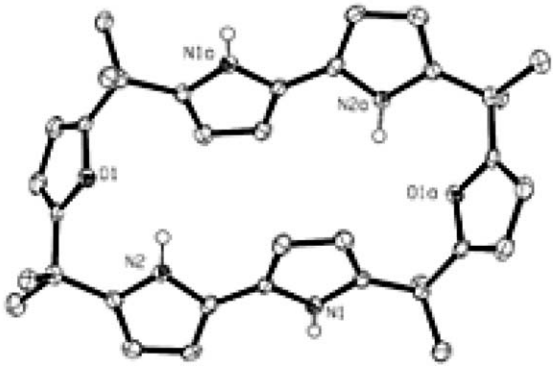
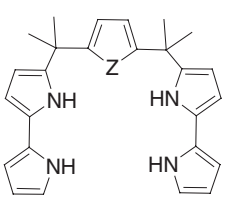


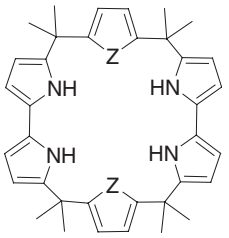
Figure 4. X-ray crystal structure of **48** (Z = O). (Reprinted with permission from 2003JA13646, Copyright 2003, American Chemical Society.)

^{1}H-NMR of these compounds showed that smaller macrocycles have weak intramolecular binding than larger ones and fewer nitrogens in the core favour stronger intramolecular H-bonding due to the increased number of acceptors. These methods provide some large-sized heterocalixarenes but are plagued by the formation of mixtures and lower yields of larger systems. The alternate targeted approach of direct head-to-tail coupling of appropriate linear oligomers or conversion of oxidative cleavage products (Section II.C) of rather easily available calix[*n*]furans may be more useful.

The bipyrrole based hybrid calix[2]bipyrrole[2]furan **48** (Z = O), obtained by $BF_3 \cdot Et_2O$ catalysed reaction of **22** (R = Me) with **47** (Z = O) selectively recognizes benzoate ion. In its X-ray structure (Figure 4) two pyrrole rings in each bipyrrole unit are oriented in opposite directions (2003JA13646).



(**47**)

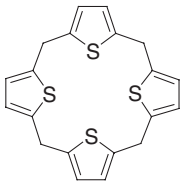


(**48**)

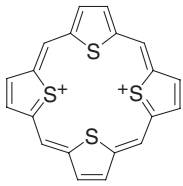
C. Chemical Transformations of Calix[*n*]furans

Since a furan ring constitutes a unique synthon (74MI1), calix[*n*]furans, for which many preparative-scale methodologies are available, have been advantageously utilized for procuring some unique and often otherwise inaccessible chemical entities, particularly some targeted receptors.

Catalytic hydrogenation (73JCS(CC)534, 76JA7414) of calix[*n*]furans provides their crown ether analogues, calix[*n*]tetrahydrofurans. In contrast to calix[4]pyrrole (**2**) (2001T2103), calix[4]furan (**7**) having methylene bridges is stable to oxygen but it oxidizes with nitric acid (88AGE406) and with DDQ (89AGE1651) to form an 18π-e aromatic dication (**26**). On reactions with H_2S and H_2Se, C_4 **7** provides calix[4]thiophene (**49**), and the selenium analogue, respectively. Since the corresponding L_4 failed to cyclize to **49**, this transformation represents the first ever synthesis of the parent calix[4]thiophene. It was oxidized with DDQ (89AGE1651) to form an aromatic dication, a sulphur-bridged annulene system **50**. However, the dication of the selenium analogue, formed on similar oxidation and characterized by its NMR (89AGE1651), could not be crystallized. Rees and co-workers have elegantly used their recently discovered conversion of 2,6-disubstituted furans into 5-acyl-3-substituted isothiazoles (2001JCS(P1)1304) in transforming octamethylcalix[4]furan and dodecamethylcalix[6]furan into various cyclophanes which in their core structures possess varied combinations of furan and isothiazole rings (2002JCS(CC)232).

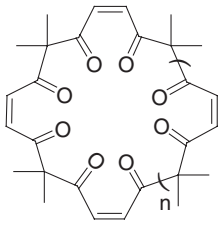


(**49**)

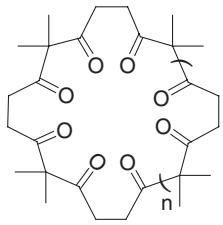


(**50**)

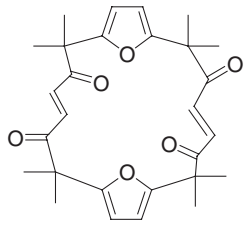
Oxidative furan-ring cleavage (81JOC4143, 2000AGE1496) of C_4 **4** and C_6 **29** using *m*-CPBA (4.2 and 6 mol, respectively) form 20-membered **51** ($n = 1$) and 30-membered **51** ($n = 3$) macrocycles embedded with *cis*-enedione chromophores as revealed by X-ray analysis in the case of the former. One of the carbonyls of each of the enedione groups deviates from the plane of the remaining π-orbital system. The *cis*-enediones can be reduced to the corresponding 1,4-diketones **52** and also isomerized to the corresponding *trans*-enediones. Using Br_2–AcOH, C_4 **4** undergoes partial furan-ring cleavage to form tetraketone **53** which in its X-ray structure shows an entirely coplanar arrangement having *trans*-enedione units (81JOC4143).



(**51**)

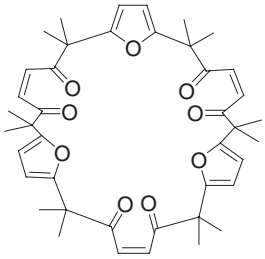


(**52**)

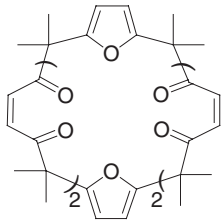


(**53**)

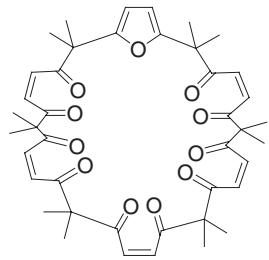
Varied stoichiometric use of *m*-CPBA affects partial or complete cleavage of calix[*n*]furans providing macrocycles containing a varied ratio of furan and enedione units (81JOC4143). C_6 **29** reacts with 6.2 mol of *m*-CPBA to give **51** ($n = 3$) and with 4.2 moles **54**, **55** and **56** are formed. Since larger calix[*n*]pyrroles and hybrid heterocalixarenes are far less accessible, the 1, 4-diketones obtained from these cleavage reactions constitute valuable precursors for such targets (2000AGE1496).



(54)



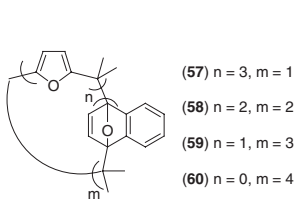
(55)



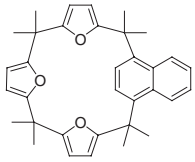
(56)

Using this approach, elusive β-unsubstituted decamethylcalix[5]pyrrole has been conveniently procured from decamethylcalix[5]furan (2002OL2695) and unlike the preconceived notion of its instability and hence difficulty of its synthesis, it has been found to be sufficiently stable to allow repeated chromatographic purification. Its X-ray structure is very similar to that of a fluorinated analogue (2000JA12061). The tetraketone **53** formed from a calix[4]furan **4**, has been converted into calix[2]furan[2]pyrrole **36** (96IC2413). Similarly calix[6]furan-derived enediones **51** ($n = 3$), **54**, **55** and **56** on reduction followed by condensation with ammonium acetate provide calix[6]pyrrole, calix[3]furan[3]pyrrole and calix[2]furan[4]pyrrole and calix[1]furan[5]pyrrole in a facile manner (2000AGE1496, 2002CEJ3148). The polyketonic macrocycles **52** ($n = 1$, 3) on reactions with hydrazine hydrate gave the corresponding homocalix[4]isopyrazole and homocalix[6]isopyrazole derivatives (2004T1895). The cavity of these C_6 systems strongly binds guests in a linear arrangement using NH moieties. Also, larger cavities would have the potential of binding anions through inclusion and thus would discriminate among guests by size more effectively than the so well-investigated calix[4]pyrrole.

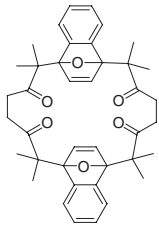
The capability of furan to undergo cycloaddition has been exploited for transforming calix[*n*]furans to some unique chemical entities. On performing the reaction of calix[4]furan 4 with benzyne in stoichiometric proportions and in a stepwise manner, Kohnke et al. (94T9113) obtained mono-**57**, *bis*-**58**, *tris*-**59** and *tetra*-**60** addition products whereas Hart et al. (82JOC4370) reported only the formation of **60**. These adducts failed to undergo deoxygenation but the hydrogenation product of the monoadduct undergoes acid-catalysed dehydration to **61** where one furan ring of C_4 **4** is replaced by a 1,4-naphthyl unit. Lack of such transformations is attributed to the rigidity of the adducts. Thus **63**, where two furan rings of C_4 **4** are replaced by 1,4-naphthyl groups, was formed from **53**, a relatively flexible system through addition of benzyne to **62** followed by catalytic hydrogenation and acid-induced dehydration (82JOC4370). The tetra adduct **60** exhibits molecular recognition in the solid state and selectively entrapped *p*-xylene when crystallized from a mixture of xylenes (94T9113).



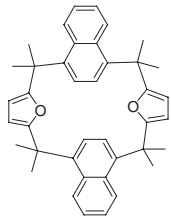
(57 - 60)



(61)

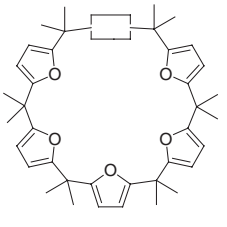


(62)

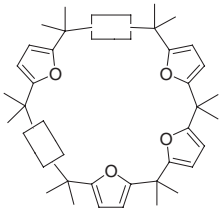


(63)

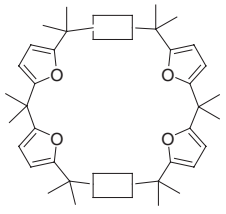
Kohnke et al., on examination of the molecular models, argued that larger-sized calix[*n*]furans being more flexible, should be better suited for aryne cycloaddition and subsequent aromatization and so investigated Diel–Alder reactions of dodecamethylcalix[6]furan(**29**) with benzyne and dimethyl acetylenedicarboxylate (DMAD) (99CEJ356). In the reaction of benzyne, a monoadduct **64a**, two *bis*-adducts **65a**, **66a** and a *tris*-adduct **67a** were isolated and differed as a function of the number and relative position of furan rings undergoing cycloaddition and the relative orientation of cycloaddition. The cycloadducts **64a**, **65a** and **66a**, on hydrogenation of the isolated double bonds followed by acid-induced dehydration were aromatized to the corresponding naphthofurophanes **64b**, **65b** and **66b**. Evidently, due to enhanced mobility of calix[6]furan, in addition to the monoadduct **64a**, even two *bis*-adducts **65a** and **66a** could also be aromatized. C_6 **29** on reaction with excess of dimethyl acetylenedicarboxylate formed a mono-adduct **64c** and four *bis*-adducts: *anti*- and *syn*-1,3-*bis*-adducts **65c**; *anti*- and *syn*-1,4-*bis*- adducts **66c**. The 7-oxanorbornadiene unit(s) of these adducts as well as their dihydro derivatives in which the olefinic bond lacking the ester functions is saturated, could not be efficiently aromatized to phthalic ester units. But these hydrogenated products undergo retero Diel-Alder reaction to form calix[6]furan derivatives **64d**, **65d** and **66d**. Thus this sequence provides a mode of access to a substitution profile in one or two furan unit(s) of **29**, which cannot be achieved by the condensation of acetone with 3,4-furandicarboxylate due to the electron-withdrawing deactivating effect of the ester groups (99CEJ356).



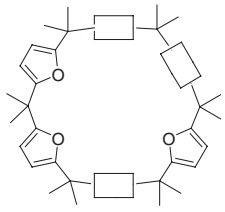
(64)



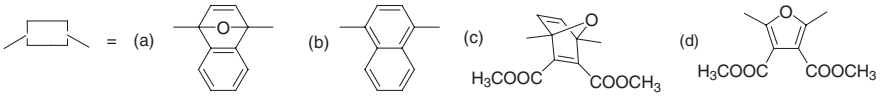
(65)



(66)



(67)



D. Interactions with Cations

Calix[*n*]furans, in general, do not show any marked reactivity towards metal cations (73JCS(CC)534, 76ICA16, 77JINC1449,85JCS(P1)973) but gas-phase interactions with proton and ammonium cation have been revealed by chemical ionization mass spectrometry (CIMS) (94JCS(P1)2881). However, octaethylcalix[4]furan (**6**) reacts with silver triflate to produce a dimeric complex $(\mathbf{6}\cdot AgSO_3CF_3)_2$ which in its X-ray structure (Figure 5) shows that the conformation and other structural parameters of the macrocycle are only slightly affected by coordination (94JA10775). It significantly exhibits a (C-H)-M triangular arrangement characteristic of a three centre–two electron interaction and this type of side-on interaction of a C–H bond as the primary interaction was unprecedented.

The disodium complex $\mathbf{36}\cdot(Na)_2(DME)_2$ obtained from the hybrid system octamethylcalix[2]furan[2]pyrrole (**36**), having alternately placed furan and pyrrole rings, undergoes metathesis reaction (96IC2413) with $CoCl_2\cdot(THF)_{1.5}$ to provide $\mathbf{36}\cdot Co(THF)_2$ complex. $\mathbf{36}\cdot(Na)_2(DME)_2$ has a flattened partial cone structure (Figure 6a) with two pyrrole rings coplanar with the mean plane of macroring and two sodium cations above and below the macroring, whereas in **36**.$Co(THF)_2$, Co^{2+} resides in the mean plane of macroring with two THF molecules coordinated above and below the mean plane to provide a distorted octahedral structure (Figure 6b).

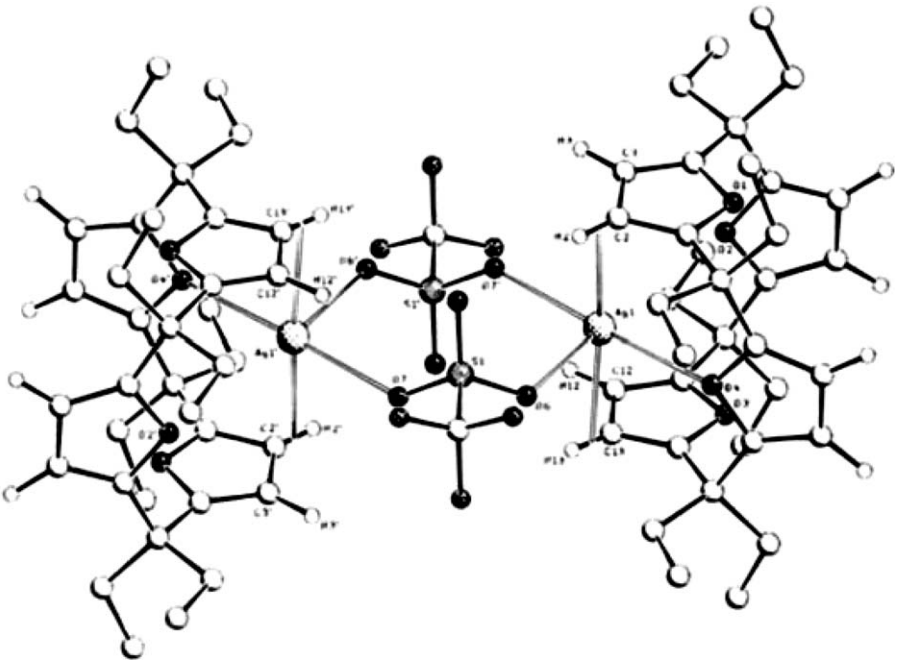


Figure 5. X-ray crystal structure of $(\mathbf{6}\cdot AgSO_3CF_3)_2$. (Reprinted with permission from 94JA10775, Copyright 1994, American Chemical Society.)

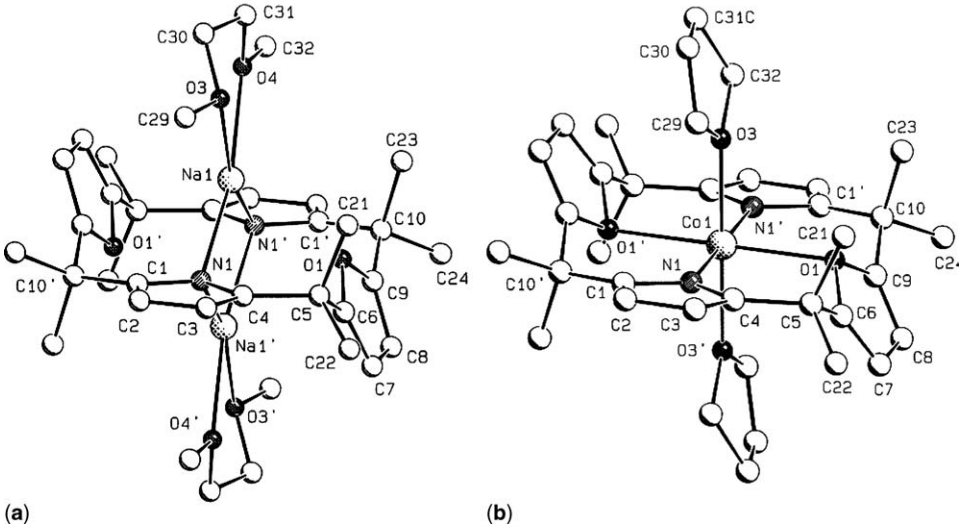
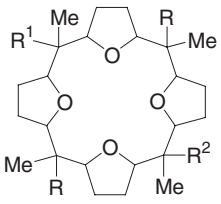
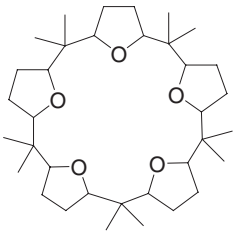


Figure 6. X-ray crystal structure of **36** · $(Na)_2(DME)_2$ (a) and **36** · $Co(THF)_2$ (b). (Reprinted with permission from 96IC2413, Copyright 1996, American Chemical Society.)

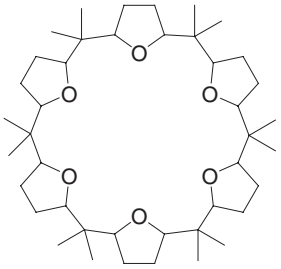
Calix[*n*]tetrahydrofurans, as compared with calix[*n*]furans, reveal better cation binding abilities. Octamethylcalix[4]tetrahydrofuran (**69**) forms a stable 1:1 complex with lithium perchlorate and thiocyanate and exhibits perturbed ^{1}H-NMR spectra on interaction with Ni^{2+} thiocyanate and perchlorate (73CC534, 85JCS(P1)973). Decamethylcalix[5]tetrahydrofuran (**72**) has selectivity for K^+ over Na^+ and Rb^+ cations and completely rejects small Li^+ and large Cs^+ cations. Ammonium and Ag^+ cations are bound favourably by this pentamer (76JA7414). A close relationship between hole size of the macrocycle and ionic diameter of the metal cation is indicated because dodecamethylcalix[6]furan (**69**) and its hydrogenated derivative **73** do not form complex metal cations (76JA7414, 85JCS(P1)973).



(**68**) R, R^1, R^2 = H
(**69**) R, R', R^2 = Me
(**70**) R, R^1 = Me, R^2 = CH_2CH_2COOH
(**71**) R = Me, R^1, R^2 = CH_2CH_2COOH



(**72**)

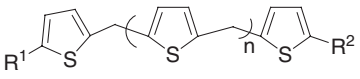


(**73**)

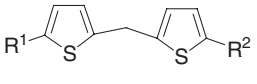
The substituents at the methylene-bridged carbons of calix[4]tetrahydrofurans show significant influence on complexation probably due to steric inhibition. The least substituted system **68** having–$CH(CH_3)$ bridges has the best complexing ability and **69** and **70** are less effective and **71** is almost ineffective for binding. All these systems show a preference for Li^+ but **68** and **69** completely discriminate between Na^+ and K^+ with a binding preference for Na^+. Across an apolar membrane, compound **68** is a most effective carrier for Na^+ and its Na^+/K^+ selectivity of 9.2 decreases in **69**. Compounds **68** and **69** which complex Na^+ rather loosely transport it more effectively revealing that the best carrier for transport is a ligand that gives a moderately stable rather than highly stable complex (76JA7414).

III. Calix[*n*]thiophenes

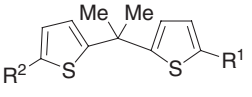
Acid-catalysed condensation of thiophene and acetone forms octamethylcalix[4]thiophene (69TL1493) in low yield as against similar facile syntheses of furan and pyrrole analogues reflecting the non-reactivity of thiophene. Unlike furan and pyrrole, thiophene also does not react with 2-isopropylolfuran – a furfuryl alcohol derivative (58CJC371). Cyclization of linear tetramers L_4 **74** and condensations of appropriate derivatives of L_2 **75** having $–CH_2–$ linkers were unsuccessful under a variety of conditions. So steric constraint at the bridged carbon of L_2 was necessary to fix intermediates in configurations suitable for cyclization and thus calix[4]thiophenes **77a** and **77b** were obtained by reactions of **76a** with **76b** and **76c**, respectively (69TL1493). However, for the synthesis of parent calix[4]thiophene (**49**), unsubstituted at the bridged carbons, furan to thiophene conversion in calix[4]furan (7) constitutes a method of choice. In the X-ray structure of **49**, four $–CH_2–$ groups lie in a plane from which thiophene rings are tilted in a way that the distance between S atoms of neighbouring thiophene rings corresponds to the spatial requirement of S (89AGE1651). The calix[1]thiophene[4]arenes **78a–d**, obtained from phenol–formaldehyde linear tetramer and thiophene derivatives in multistep procedures, bind *N*-methylpyridinium cation (99H2807, 2001JHC293).



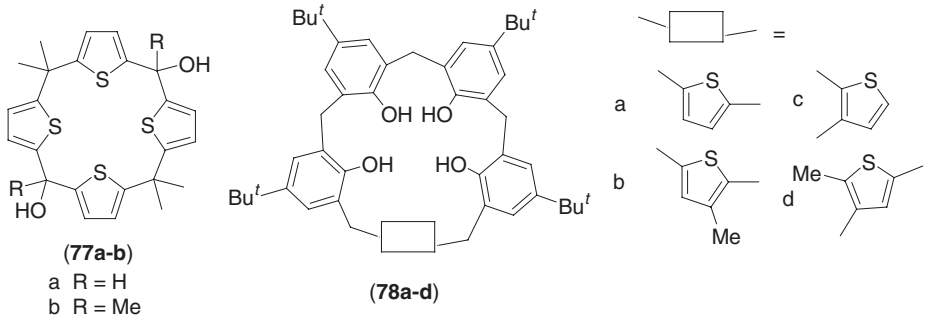
(**74**) a, R^1, R^2 = $COOCH_3$
b, R^1, R^2 = COOH
c, R^1, R^2 = H



(**75**) a, R^1, R^2 = H
b, R^1, R^2 = CHO
c, R^1, R^2 = COMe



(**76**) a, R^1, R^2 = H
b, R^1, R^2 = CHO
c, R^1, R^2 = COMe



Using sodium sulphide-induced conversion of 1,3-butadiyne chromophore to a thiophene ring, [*n*]rotanes **79** provide a unique and structurally intriguing category of C_5, C_6 and C_8 calix[*n*]thiophenes **80** ($m = 0, 1, 3$) possessing cyclopropylidene bridges (95AGE781). Hexacyclopropylidenecalix[8]thiophene (**80**, $m = 1$), in its X-ray structure (Figure 7) showed a chair like conformation with a centre of inversion. Each cyclopropane ring has a close to optimal orientation for conjugation only with one of its neighbouring thiophene moieties. This unusual conformation with three sulphur atoms above and three below the equatorial plane probably results as an energetic compromise between the mutual repulsions of the sulphur atoms and a maximum conjugation between the cyclopropane and thiophene fragments.

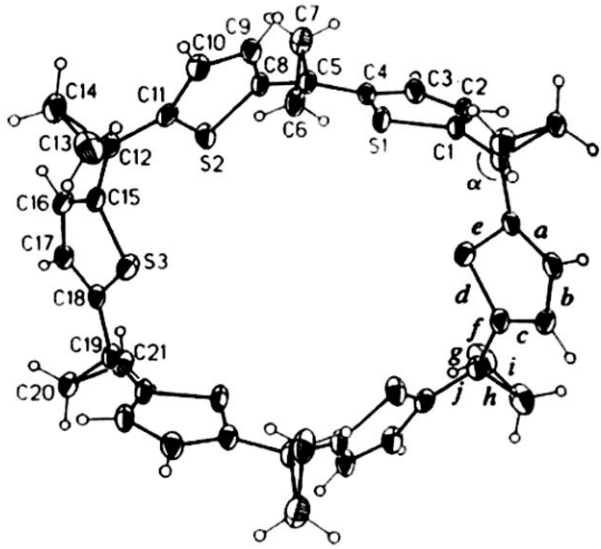
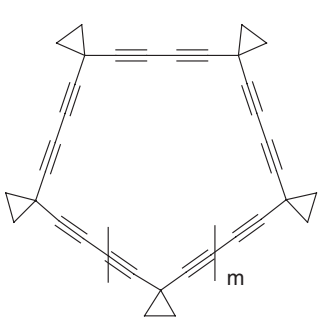
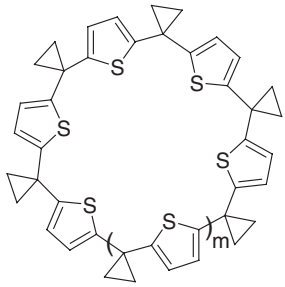


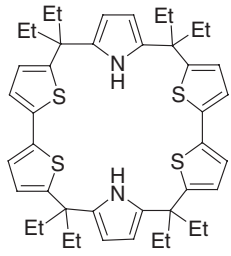
Figure 7. X-ray crystal structure of **80** ($m = 1$). (Reprinted with permission from 95AGE781, Copyright 1995, John Wiley & Sons Inc.)



(79)



(80)



(81)

The bispyrrole-based hybrid calix[2]bipyrrole[2]thiophene **48** (Z = S), obtained by $BF_3 \cdot Et_2O$-catalysed reaction of **23** (R = Me) with **47** (Z = S), selectively recognizes benzoate ion. In its X-ray structure (Figure 8), each bipyrrole unit with its pyrrole units facing in the same direction is bound via two NH—O interactions with tetrahydrofuran, the solvent of crystallization (2003JA13646). Similarly, bithiophene containing hybrid heterohexamer **81** was obtained by $BF_3 \cdot Et_2O$-catalysed reaction of 1,7-*bis*-(2′-pyrrylmethyl)bithiophene with 1,7-*bis*[(α-hydroxy-α,α-diethyl)methyl]bithiophene. Condensation of acetone with 1,7-*bis*(2′-pyrrylmethyl)bithiophene formed super expanded octameric and decameric systems (2002TL9493).

For providing additional coordination sites, heteroatom-bridged calix[4]thiophenes have been synthesized. A sulphur-bridged calix[4]thiophene **82** was obtained in 1% yield from 2,5-*bis*anion of thiophene and S_2Cl_2 (97JCR(M)555).

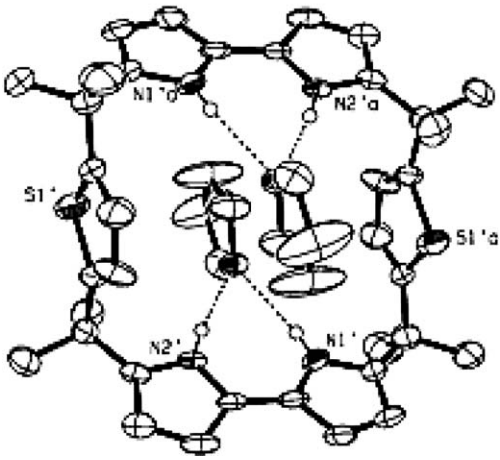
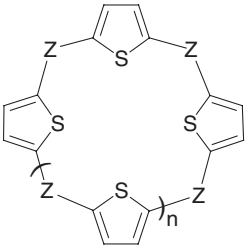
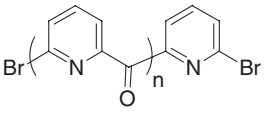


Figure 8. X-ray crystal structure of **48** · $(THF)_2$ (Z = S). (Reprinted with permission from 2003JA13646, Copyright 2003, American Chemical Society.)

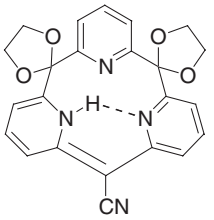
Silicon-bridged calix[4]thiophene **83** was obtained in a straightforward manner by condensation of dichloromethylsilane with lithiated 2,2-*bis*(2′–thienyl)-2-silapropane (73TL4043). Lithiated thiophene on similar reaction gave **83** (18%) and **84** (17%) (95AGE661). Compound **83** in its X-ray structure displays a 1,3-anti-arrangement of thiophene units. Phosphorous-bridged calix[4]thiophene **85** (17%) was formed by using dichloro phenylphosphine. Because of its relatively restricted mobility, its two isomers were revealed in its NMR spectrum (95JOC7406).



(**82**) Z = -S-, n =1
(**83**) Z = -Si(Me)$_2$-, n =1
(**84**) Z = -Si(Me)$_2$-, n = 2
(**85**) Z = -PPh-, n =1



(**86**) a, n = 1
b, n = 2



(**87**)

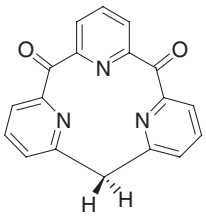
IV. Calix[*n*]pyridines and Related Systems

A. General

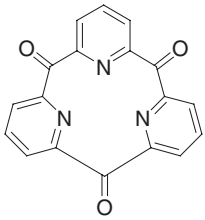
Incorporation of π-electron-deficient N-electron-rich pyridine in the core of calixarenes generates π-electron-deficient cavities with Lewis acid acceptor character. Electron deficiency of such systems has been further increased by carbonyl bridges. Newkome (87JCS(CC)854, 86JA6074, 90JOC5714) designed calix[*n*]pyridine systems **89** and **90**, which could constitute ideal structures to probe electronic and steric effects of N electrons within highly rigid electron-deficient cavities. Some hetero-atom-bridged calix[*n*]pyridines are also reported (2002TL7945, 2002JCS(CC)1686, 72JCS(CC)1059). The synthesis of these heterocalixarenes would not be possible normally through traditional electrophilic procedures and hence alternate methodologies have been developed. However, some octahydroxycalix[4]pyridines having nitrogens at the upper rim, have been formed by reactions of 2,6-dihydroxypyridine with aldehydes (2001CEJ465). Some calix[4]pyridine and calix[*n*]pyridine[m]pyrrole/arene systems have been obtained by invoking pyrrole to pyridine ring homologation in calix[4]pyrrole system (98JCS(CC)9, 88AGE406, 99OM606). The synthesis, structures and physico-chemical behaviour of these systems are discussed.

B. Direct Synthesis

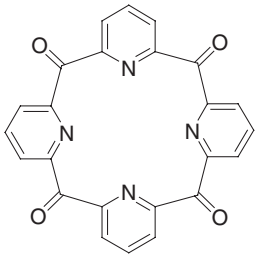
Diketone **86b** formed from 2-lithio-6-bromopyridine and 2,6-*bis*(ethoxy carbonyl)/dicyano-pyridine, after ketalization was cyclized with lithioacetonitrile to form **87**. Alcoholic HCl hydrolysis of **87** followed by SeO_2 oxidation of crude product **88** (86JA6074) and direct acidic hydrolysis of **87** under aerobic conditions (90JOC5714) give the triketonic calix[3]pyridine **89** in overall 50% yield. *m*-CPBA-mediated oxidation of **87** gave diketal of **89**, which could be partially deketalized to monoketal and completely ketalized to triketal (90JOC5714). Ketalized **86a** on reaction with lithioacetonitrile undergoes facile metal-templated macrocyclization to afford **91** (87JCS(CC)854). Hydrolysis of **91** to **92** followed by SeO_2 oxidation affords tetraketonic calix[4]pyridine (**90**). Alternatively, *m*-CPBA oxidation of **91** and subsequent hydrolysis affords **90**.



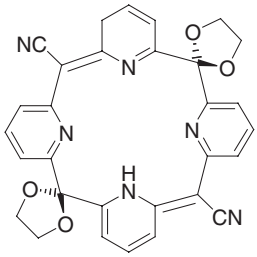
(**88**)



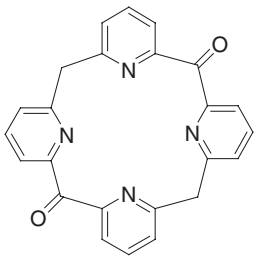
(**89**)



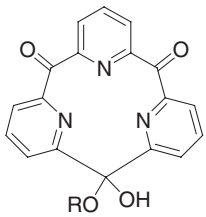
(**90**)



(**91**)



(**92**)



(**93**) a, R = Me
b, R = Et

These heterocalixarenes possessing unusually crowded cavities with 3 or 4 nitrogen electron lone pairs and having all sp^2 carbons are expected to be essentially planar. But in its X-ray structure, **89** is distinctly non-planar, due predominantly to lone pair–lone pair repulsions. The distortion from planarity leads to a conformation in which two lone pairs tip out of plane on one side of the molecule and the third tips in

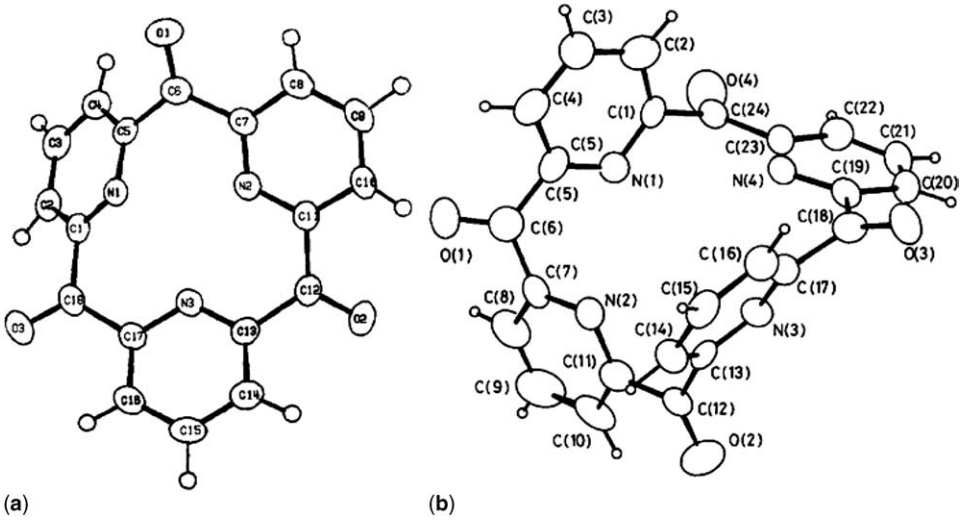
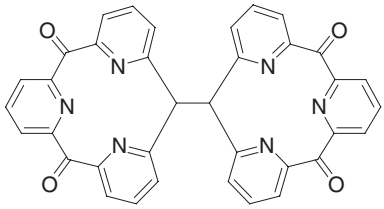


Figure 9. X-ray crystal structures of (a) **89** and (b) **90**. (Reprinted with permission from 86JA6074, Copyright 1986, American Chemical Society.)

the opposite direction (Figure 9a) (86JA6074). Its energy minimized structure is in close agreement with its crystal geometry where the three N lone pairs repel each other due to their directed juxtapositions (90JOC5714). Likewise, tetraketonic calix[4]pyridine [**90**] is severely distorted from planarity and has a saddle shape. The nitrogen lone pairs point alternately above and below the best plane of four nitrogen atoms which form an approximate square (Figure 9b) (87JCS(CC)854). Initial macrocyclization products **87** and **91** in their X-ray structures show strong NH…N interactions and fixed tautomeric forms (87JCS(CC)854, 86JA6074).

The contiguously placed pyridine and carbonyl units and intercepting sp^3-hybridized carbon in the above calixpyridine systems elaborate unprecedented chemical reactivity at such bridged sp^3 and sp^2 carbons of calixarenes. The triketone **89**, even on crytallization from methanol instantaneously forms the hemiketal **93a** (90JOC5714), because on consequent conversion of one sp^2 C to sp^3 C unfavourable N,N interactions are released. The molecular structure of the hemiketal is again severely distorted from a planar conformation and an intermolecular H-bond exists between the hemiketal H and an O of the carbonyl of the adjacent molecule. The hydrolysis of **87**, under even inert atmosphere, provides trione **89** (20%) and the dimer **94** (80%) which on DDQ dehydrogenation as well as on aeration forms an ethylene bridge. Under aerobic acidic conditions, **87** hydrolyses to unstable **88** which on SeO_2 oxidation gives **89**. Even crystallization of **88** forms a mixture of **89** and **94**. The results of these hydrolytic reactions and existence of fixed tautomeric forms **87** and **91** point to the reactivity at sp^3 carbon, where due to the lability of H, the radical generated could dimerize or trap oxygen to generate a hydroperoxide leading to ketone or alkene (90JOC5714).

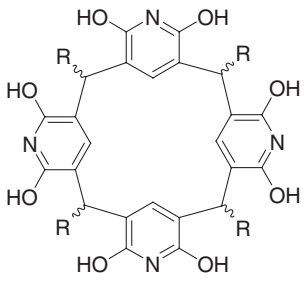


(**94**)

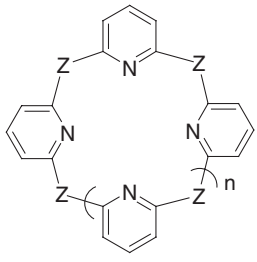
The nitrogen lone-pair directed into the cavity and the inherent slight conformational mobility as indicated by a CPK model could facilitate complexation of **89** with $CuCl_2$ in anhydrous ethanol–HCl to form a complex **93b**. $CuCl_2$ which elaborates a cone conformation (90JOC5714). These results point to both the anticipated mobility of non-cone conformation and carbonyl reactivity of **89**.

2,6-Dihydroxypyridine, unlike pyridine, undergoes acid-catalysed condensation with aliphatic and aromatic aldehydes to form various conformational isomers of octahydroxycalix[4]pyridines (**95**) (2001CEJ465). As compared with other calixpyridines, these systems have stereogenic methine groups and the nitrogen at the upper rim is flanked by two hydroxyl groups. This structural arrangement suited for intermolecular hydrogen bonding generates head–head dimers which have been shown to incapsulate small carboxylic acid molecules in their cavity (2004JA9669).

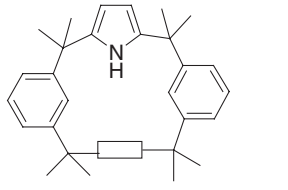
Since replacement of carbon bridges of relatively rigid calixpyridines by sulphur or nitrogen ones should increase their flexibility and thereby their coordination ability, which may be augmented by these heteroatoms, such systems have been synthesized. The S-bridged calix[3]pyridine C_3 **96** was formed by straightforward intermolecular condensation of 6-chloropyridine-2thione and its X-ray analysis established a non-planar conformation (72JCS(CC)1059). In a convenient one-pot reaction of 2,6-dibromopyridine and sodium hydrosulphide, a mixture of calix[*n*]pyridines C_3 **96**, C_4 **96** and C_5 **96** is formed. The flexibility of these systems allowed their facile complexation with $CuBr_2$ as against limited coordination ability of calix[n]pyridines and these thiacalix[*n*]pyridines coordinate to copper ion through nitrogen and sulphur atoms to give multinuclear complexes whose structures have been determined by X-ray crystallography and NMR spectra (2002JCS(CC)1686).



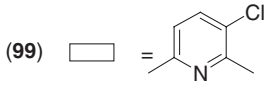
(**95**)



(**96**) Z = S
(**97**) Z = NMe



(**98**)



(**99**)

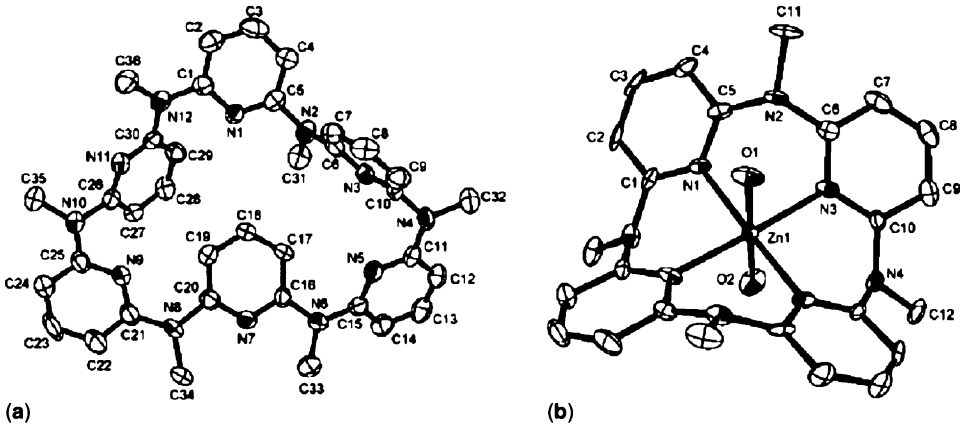


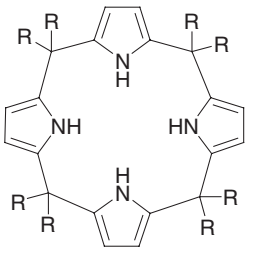
Figure 10. X-ray structures of (a) **97** ($n = 3$) and (b) **97** ($n = 1$) $\cdot ZnCl_2$ complex. (Reprinted with permission from 2002TL7945, Copyright 2002, Elsevier.)

Azacalix[*n*]pyridines C_4 **97** (1.5%) and C_6 **97** (10.1%) have been synthesized by one-step Pd-catalysed aryl amination of 2,6-dibromopyridine with 2,6-*bis*(methylamino)pyridine. The cyclocondensation of 2-bromo-6-(methylamino) pyridine gave only C_6 **97** (8%) (2002TL7945). The electrostatic repulsions between nitrogens seem to inhibit the formation of tetramer, the main product in aryl amination of 3-bromo-*N*-methylaniline. In the solid state, C_6 **97** adopts an unsymmetrical distorted conformation (Figure 10a) attributed to the electrostatic repulsion between the N atoms in the cavity. In the C_4 **97** $\cdot ZnCl_2$ complex, Zn^{2+} is included in the cavity and lies in the plane determined by the four pyridine N atoms and the complex adopts an S_4 conformation (Figure 10b) in which each of the pyridine ring is alternately twisted from side-to-side to the plane (2002TL7945).

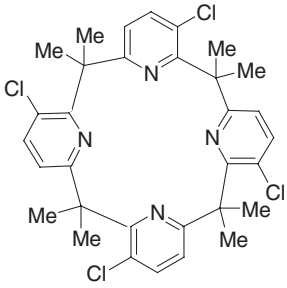
C. Synthesis Through Ring Expansion

The ring expansion of pyrrole(s) of so easily available meso-octamethyl calix[4]pyrrole (**100a**) to pyridine(s) by invoking dichlorocarbene insertion and transition metal assisted reactions of carbon monoxide constitute synthetic methodologies of relevance in forming, unlike earlier approaches, calix[4]pyridine and hybrid calix[*n*]pyrrole[*m*]pyridine systems bearing sp^3-hybridized bridges. The reaction of dichlorocarbene with octamethylcalix[2]benzene[2]pyrrole (**98**) gave octamethylcalix-[2]benzene[1]-3-chloropyridine[1]pyrrole (**99**) which elaborates a flattened partial cone conformation in the solid state (2002CEJ1134). In a reaction of **100a** performed in dioxan solvent using 15 equivalents of sodium trichloroacetate, a mixture of calix[1]3-chloropyridine[3]pyrrole (**104**) and calix[2]3-chloropyridine[2]pyrrole (**103**) systems (2.4:1) are formed (98JCS(CC)9). When the same reaction conditions are employed using dimethoxyethane, a mixture of (**103**) and

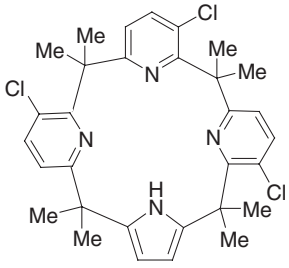
calix[3]3-chloropyridine[1]pyrrole (**102**) and calix[4]3-chloropyridine (**101**) is obtained in equal proportions. On adding 3–6 equivalents of the carbene source in a sequential manner, **103**, **102** and **101** are obtained in 65%, 42% and 26% yields, respectively. On using 5 equivalents of carbene precursor the formation of only **104** has been reported (2002CEJ1134). Compound **101** adopts a flattened partial cone conformation in the solid state. The crystals of **103** reveal two crystallographically distinct molecules in the unit cell and both adopt a cone conformation in the solid state such that potential NH…N hydrogen bonds are formed. Likewise, there are two molecules of **102** per asymmetric unit and both adopt strikingly different conformations. In one of these molecules, alternate rings are either nearly parallel or nearly perpendicular as in the case of **101**. The X-ray structure of **104** (2002CEJ1134) revealed a flattened partial cone conformation (Figure 11a) and crystallizes in different crystal packings, depending upon the solvent of crystallization. From CH_2Cl_2 – hexane, 104 crystallizes in a dimeric form stabilized by NH…Cl interactions (Figure 11b) and from MeOH, it crystallized as an infinite chain, stabilized by NH…Cl and NH…O interactions (Figure 12). It elaborates dimeric (CH_2Cl_2/hexane) and infinite chain (MeOH) structures stabilized by NH…Cl and NH…O, NH…Cl interactions, respectively.



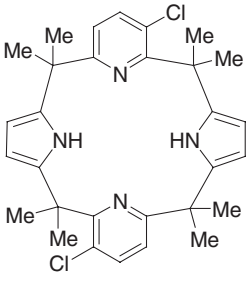
(**100**) a R = Me
b R = Et



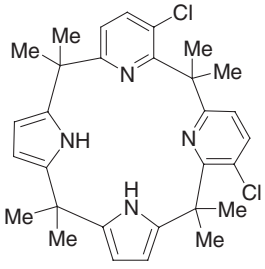
(**101**)



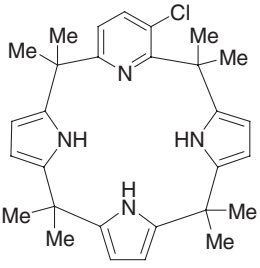
(**102**)



(**103a**)



(**103b**)



(**104**)

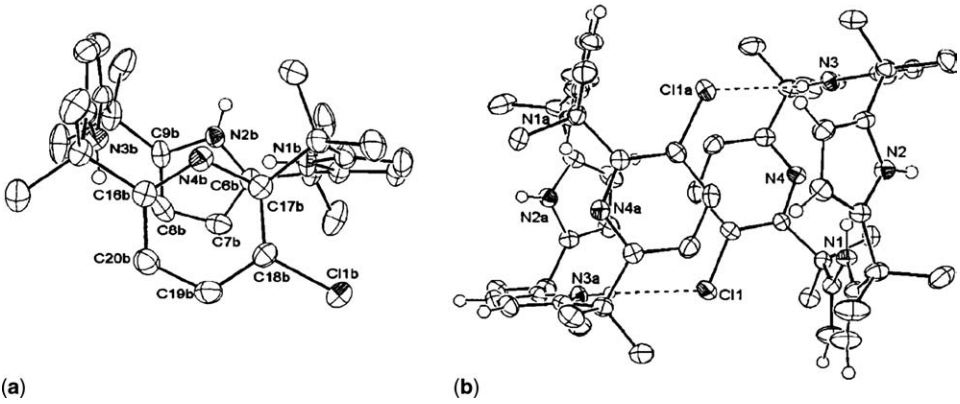


Figure 11. X-ray crystal structure of **104** (a) shows a flattened cone conformation and (b) shows the dimeric form. (Reprinted with permission from 2002CEJ1134, Copyright 2002, John Wiley & Sons Inc.)

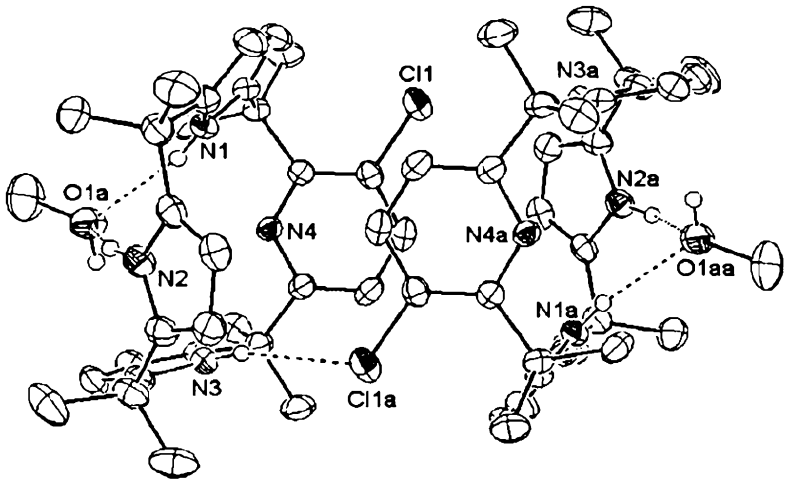
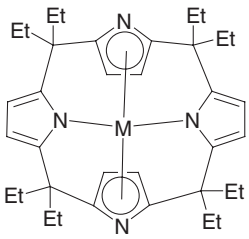


Figure 12. X-ray crystal structure of **104** as crystallized from MeOH. (Reprinted with permission from 2002CEJ1134, Copyright 2002, John Wiley & Sons Inc.)

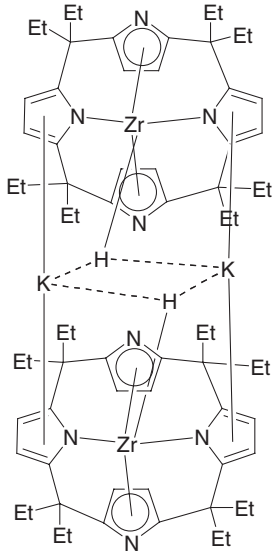
Metal-assisted homologation of up to two pyrrole rings of meso-octaethylcalix[4]pyrrole (**100b**) to pyridine rings even having alkyl and alkenyl groups has been achieved with high selectivity, controlled regiochemistry and in good yield at a multigram scale (95JA2793). The bimetallic zirconium-alkali metal hydrido derivative **106** formed from **105a** on reaction with carbon monoxide produces a product which on hydrolysis provides octaethylcalix[1]pyridine[3]pyrrole (**107a**) in a synthetically useful manner in 40–60% yield. Here the role of oxophilic Zr and K on

enhancing the carbenium ion nature of the formyl functionality pointed to the formyl carbon at position 3 of the evolved pyridine ring. The regiochemistry of homologation was confirmed by a reaction of CO with Zr alkyl derivatives of **100b** formed by hydrozirconation of ethylene and acetylene with **106**, where the products **107c** and **107d** having ethyl and vinyl substituents at position 3 firmly define the above regioselectivity.

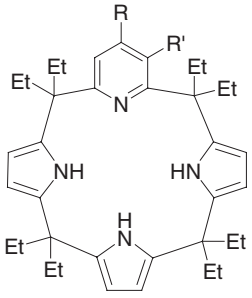


(**105**)

a M = Zr
b M = NbMe

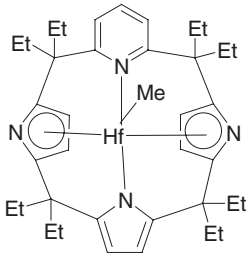


(**106**)

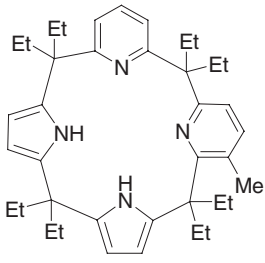


(**107a-d**)

a R, R' = H
b R = Me, R' = H
c R = H, R' = Et
d R = H, R' = -CH=CH_2



(**108**)



(**109**)

Using metals other than Zr, different regiochemistries of homologation of **100b** and homologation of a second pyrrole ring have been achieved. **105b** on a sequence of reactions with CO and hydrolysis provides **107b** having pyridine substituted at position 4. Evidently, attack of the electrophilic acyl carbenium ion to the β-position of pyrrole may be due to a different orientation and binding mode of the pyrrole to the metal. For the second homologation, lithiation of pyrrole ring of **107a** was followed by metalation with $HfCl_4$ and methylation with methyl lithium to form **106**, which on reaction with CO and hydrolysis gave **109**. Although the reaction was not successful with Zr, the use of Hf also invokes the same regiochemistry. In the X-ray structure of **109**, methylpyridine and pyrrole rings opposite to each other are nearly parallel and also perpendicular to the mean plane through the N atoms. The second pair of rings is approximately perpendicular to each other. The two pairs are orientated towards the opposite sides of the N_4 plane (Figure 13).

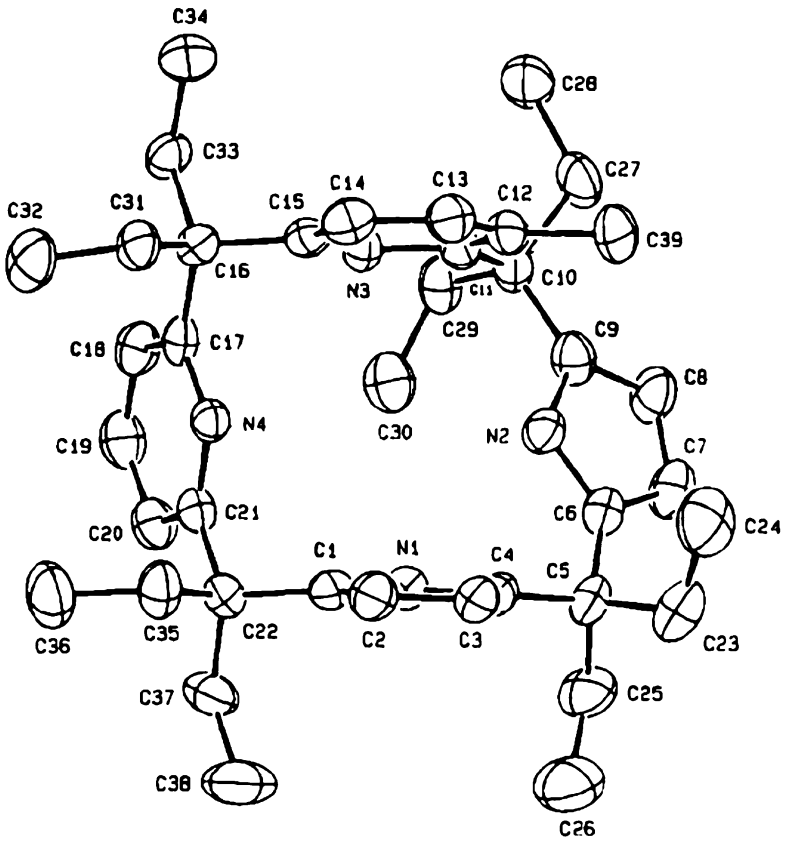
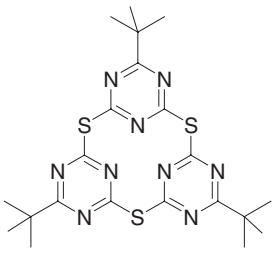


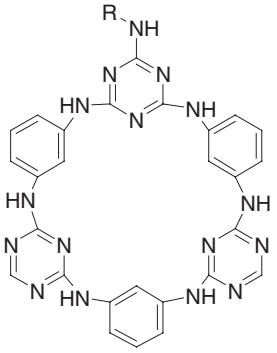
Figure 13. X-ray structure of **109**. (Reprinted with permission from 95JA2793, Copyright 1995, American Chemical Society.)

V. Triazine-Based Heterocalixarenes

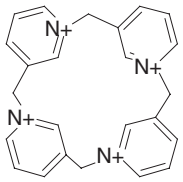
Calix[*n*]triazines represent another dimension of the electron-deficient heterocalixarenes as the electronic complement to the π-basic calixarenes and as recognition systems for electron-rich guests. S-linked calix[3]triazine (**110**) was obtained in a straightforward reaction of 2,4-dichloro-6-t-butyl-1,3,5-triazine with sodium sulphide (97TL7639). It elaborates a disc-shaped flat structure in X-ray studies, while its molecular modelling indicates a high degree of conformational mobility. Each triazine ring participates in π- stacking interactions with neighbouring molecules.



(**110**)



(**111**)



(**112**)

Since melamine is bestowed with structural elements providing both H-bond donor and acceptor sites for recognition of biological molecules such as uracil, carbohydrates, etc., triaminotriazine and *m*-phenylenediamine scaffolds have been incorporated in calix[3]1,3,5-triazine[3]arene (**111**) (2003TL1359). It has been synthesized by a stepwise sequence of reactions of cyanuric acid and monoprotected *m*-phenylene diamine, involving protection—deprotection modes to form the precursor linear hexameric oligomer which is cyclized and processed to form **111**. However, it lacked the expected binding ability. It has been argued that the rigidity of the molecule as revealed in its modelling studies does not facilitate distortions necessary for H-bonding with guests.

VI. Cationic and Betaine Heterocalixarenes

A. General

The increasing interest in anionic recognition has focused attention towards synthetic receptors possessing positively charged moieties which could induce non-covalent

electrostatic interactions with anions and the consequent recognition. In the frame of heterocalixarenes, pyridinium cations as such and imidazolium cations in combination with *m*-phenylene, pyridine and 1,2,4-triazole species have been incorporated. The protic 1,2,4 (1*H*)-triazole constituents of these heterocalixarenes have been deprotonated to anions and in case both charges balance each other, betaine heterocalixarenes are formed. Here, syntheses, structures and interactions of some such systems are elaborated.

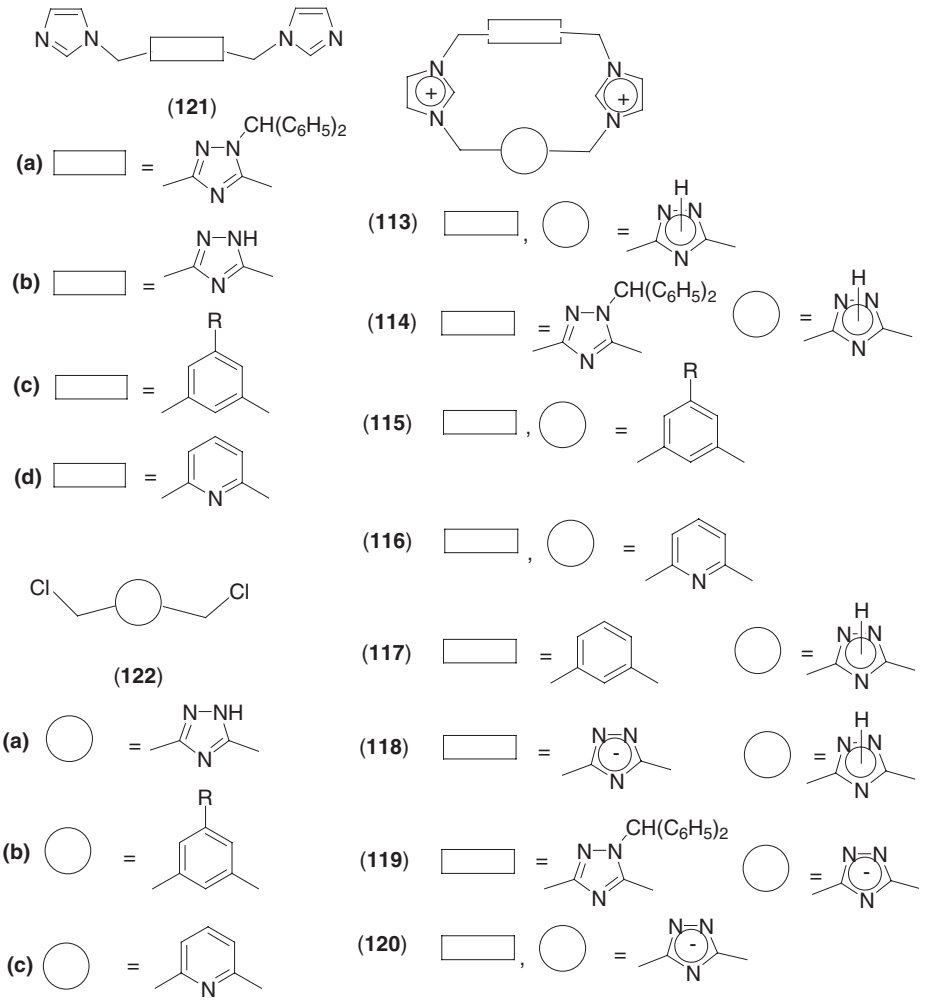
B. Calix[4]pyridinium Cations

A unique heterocalixarene possessing a quaternary calix[4]pyridinium tetracation core was formed along with some linear oligomers in self-N-alkylation of 3-bromomethyl pyridine generated *in situ* from its hydrobromide and crystallized from water as a hydrated tetrabromide (**112**) (98JCS(CC)181). Its crystal structure reveals a 16-membered macroring having four pyridine nitrogen atoms with positive charge in almost one plane. Of the four bromide ions, two each are located inside and outside the macrocycle. It binds tricarboxylates preferably the acyclic ones, in 1:1 stoichiometry.

C. Calix[2]imidazolium[2]1,2,4-triazole and Related Systems

For the synthesis of dicationic heterocalixarenes **113**–**117**, possessing two 1,3-imidazolium rings and two (i) 3,5-(1,2,4-triazole) (**113**, **114**), (ii) 1,3-phenylene (**115**), (iii) 2,6-pyridine (**116**) rings and (iv) a combination of 1,3-phenylene and 3,5-(1,2,4-triazole) rings (**117**), a (3 + 1) convergent approach has been employed.

The condensation of **121a** with 3,5-dichloromethyl-1,2,4-triazole (**122a**) formed **114** which on deprotection gave the parent calix[2]imidazolium[2]triazole system **113** (95JCS(CC)1239, 2002CEJ474). Similarly, other dicationic heterocalixarenes could be obtained by direct macrocyclizations of *bis*-imidazole derivatives **121b**–**d** with dihalides **122a**–**c**. The treatment of **113** and **114** with anion-exchange Amberlite IRA-40 resin (OH^- form) followed by acidification to pH 6 with aq. HPF_6 gave dipolar systems **118** and **119**, respectively. Calix[2]imidazolium[2]triazole (**113**) with Amberlite-IRA-40 resin formed quadrupolar betaine **120** – an unconventional heterocalixarene constructed by both highly π-excessive and π-deficient heteroaromatic moieties linked in a 1,3-alternating fashion. The bis-betaine **120** on controlled acidification provides **118** as well as **113** and reacts with *n*-butyl iodide to form the corresponding dication [2002CEJ434, 96T15171). The molecular structures of **118** and **120** were confirmed by X-ray crystallography (95CC1239, 2002CEJ474). In their ^{1}H-NMR spectra, the expected shielding effect for $-CH=N^+$ and $-CH_2-$ as compared with the same in **113**, is distinctly revealed with $\Delta\delta$CH and $\Delta\delta CH_2$ for **118** and **120** being −0.26, −0.87 ppm and −0.12, −0.44 ppm, respectively (96T15171).



The condensations of 1,3-*bis*-(halomethyl)benzenes **122b** (R = H, Bu^t) with derivatives of **121c** provided the corresponding calix[2]imidazolium[2]arenes **115**. **2X**$^-$ (a, R = H; b, R = Bu^t) in good yields (99JCS(CC)295). The addition of TBACl or TBABr further enhanced the yields, evidently due to anion template assistance (99OL1035). Even the halide anions (Cl$^-$, Br$^-$), generated *in situ*, during macrocyclization act as self-template by the formation of intermediates having C–H…Cl$^-$ hydrogen bonds and thereby optimal conformation favouring the cyclization step. The molecular recognition motifs for anion templation involve the interaction of a multicentred chloride ion with π-deficient and aromatic moieties as hydrogen-bond donors. Through kinetically investigated quantification of the rate of macrocyclization of the intermediate monocation **123**, it was found that in the presence of $Bu_4N^+Cl^-$, the rate is increased up to 10 times (2002JOC8463).

In the formation of **113**, an anion template effect was not visible because of the diminished ability of the 1,2,4-triazole nucleus to form H-bonds, but the enhanced

reactivity of 3,5-*bis*(chloromethyl)triazole (**122a**) modulates the macrocyclization reaction by accelerating the rate of the condensation step. Accordingly, of the two modes of preparing calix[2]imidazolium[1]1,2,4-triazole[1]arene system **117** · $2Cl^-$ by condensation of **121b** with **122b** or condensation of **121c** with **122a**, the latter provides the product in higher yield (99OL1035).

Analysis of X-ray structures revealed that the dications **115a** · $(Cl^-)_2 \cdot (H_2O)_2$ and **115b** · $(Cl^-)_2 \cdot (H_2O)_{3.5} \cdot (CH_3CN)_{0.5}$ adopt a partial cone and a cone conformation, respectively (99JCS(CC)295), and their macrocyclic cavity is a square of about 5 Å per side. In **115a** · $(Cl^-)_2 \cdot (H_2O)_2$, chloride anions occupy an outer position above and below the main plane defined by the methylene spacer groups and are H-bonded in a three-centred manner between 1,3-xylyl H-6 and acidic C_2–H of the imidazolium cation (Figure 14a). There are weak interactions with water. The X-ray structure of **115b** · $(Cl^-)_2 \cdot (H_2O)_{3.5} \cdot (CH_3CN)_{0.5}$ reveals two different cations, of which molecule **I** has a propensity to form H-bonds with one of the chloride counter anions; meanwhile molecule **II** interacts with one water molecule (Figure 14b).

The calix[2]pyridine[2]imidazolium dication **116** · $(Br^-)_2$ system (2001OM1276) was designed as a macrocyclic (heterocalixarene) carbene precursor for investigating transition and main group metal complexation and was again synthesized by (3 + 1) convergent condensation of 2,6-*bis*(imidazolmethyl)pyridine (**121d**) and 2,6-*bis*(bromomethyl)pyridine (**121c**). On treatment with CrO_3 or ammonium hexafluorophosphate, both Br^- could be exchanged to form **116** · Cr_3O_{10} and **116** · $(PF_6)_2$ which in their X-ray structures (Figures 15a and b) revealed, respectively, distorted asymmetric 'eclipsed chair' and 'staggered chair' conformations attributed to different counter-anions. Both exhibit box-shaped cavities and hydrogen-bonded network in the solid state. In **116** · $(PF_6)_2$, fluorine atoms of the PF_6 anion and in **116** · Cr_3O_{10}, the oxygen atoms of the anion form hydrogen bonds with H of both bridge methylene and imidazolium cation. **116** · Cr_3O_{10} has many more H-interactions than **116** · $(PF_6)_2$, resulting in an irregular geometry of the dication portion.

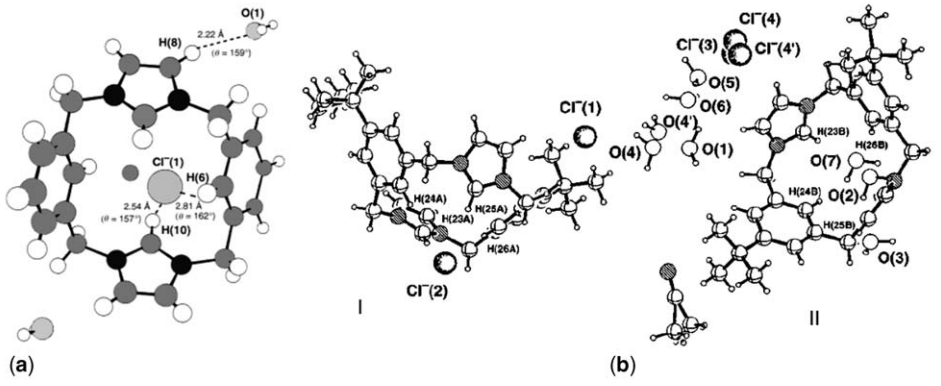


Figure 14. X-ray structure of (a) **115a** · $(Cl^-)_2 \cdot (H_2O)_2$ and (b) **115b** · $(Cl^-)_2 \cdot (H_2O)_{3.5} \cdot (CH_3CN)_{0.5}$. (Reprinted with permission from 99JCS(CC)295, Copyright 1999, Royal Society of Chemistry.)

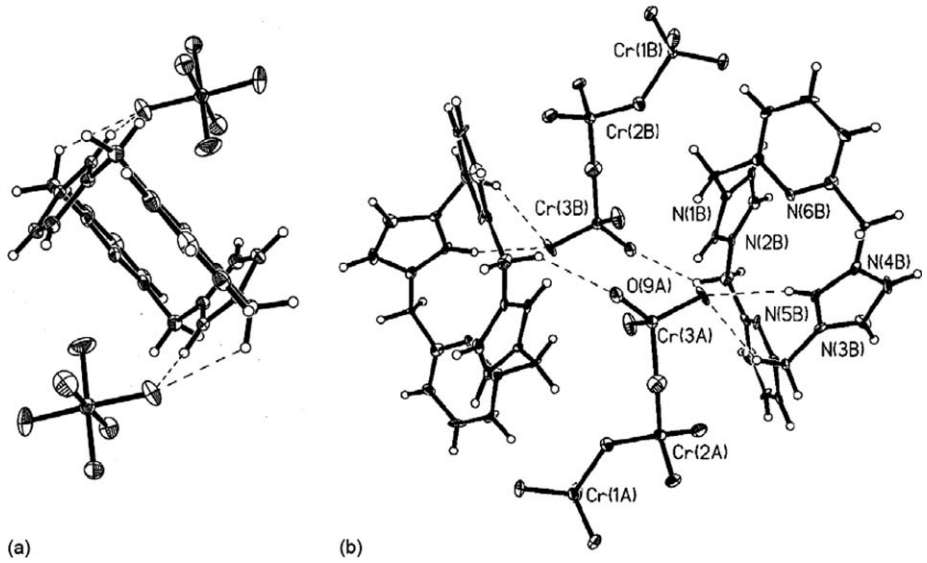
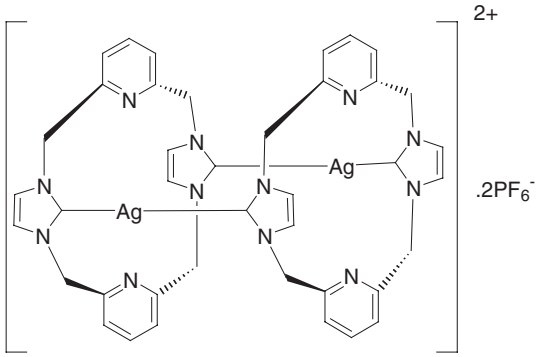


Figure 15. X-ray crystal structures of (a) $\mathbf{116 \cdot (PF_6)_2}$ and (b) $\mathbf{116 \cdot Cr_3O_{10}}$. (Reprinted with permission from 2001OM1276, Copyright 2001, American Chemical Society.)



(**123**)

With Ag_2O, $\mathbf{116 \cdot (PF_6)_2}$ affords an unprecedented dimeric silver carbene complex **123** which in its X-ray structure (Figure 16) is symmetric about an inversion centre. In its ^{1}H-NMR, all the signals shift upfield as compared to those in the precursor $\mathbf{116 \cdot 2PF_6^-}$ with the absence of a resonance for the imidazoium cation C_2–H where carbon in the ^{13}C-NMR reveals a broad peak at 183 ppm – characteristic of a carbene moiety (2001OM1276). Surprisingly, the role of such macrocyclic carbene precursors in mimicking thiamine catalysed reactions has not been investigated.

The above investigations on charged heterocalixarenes were conveniently extended to hexameric and octameric systems with enlarged cavities, employing (5 + 1) and

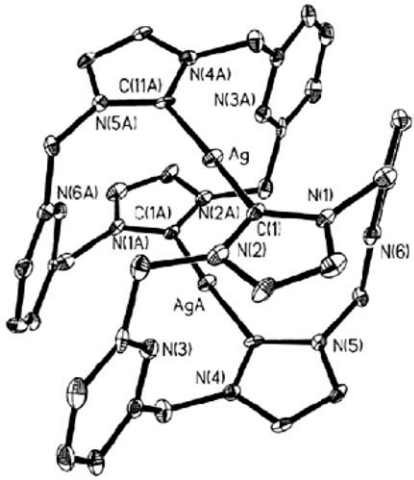
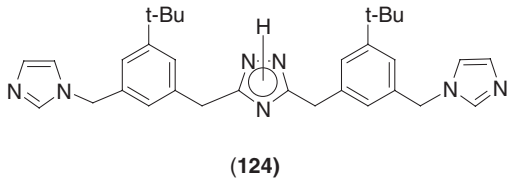
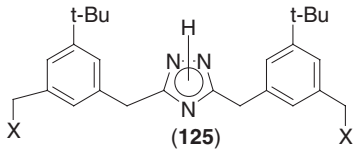


Figure 16. X-ray crystal structure of **123**. Hydrogen atoms and PF_6^- are omitted for clarity. (Reprinted with permission from 2001OM1276, Copyright 2001, American Chemical Society.)

(5 + 3) convergent stepwise approaches. Thus on coupling **124** with **122a** and **125**, the heterocalixarenes **126a** and **127a**, respectively were obtained (2001JOC2281) in relatively lower yields. In these reactions, the protonation of **124** has an adverse effect on its reactivity and similarly poor solubilities of protonated **124** and dicationic products **126a**, **127a**, made their separation difficult. The anion template effect was not visible in both these condensations.

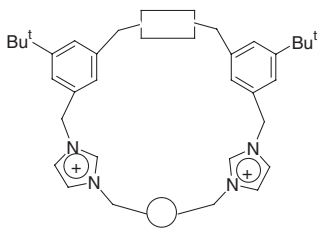


(**124**)

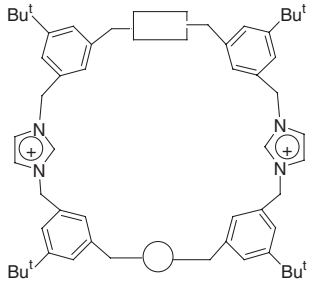


(**125**)

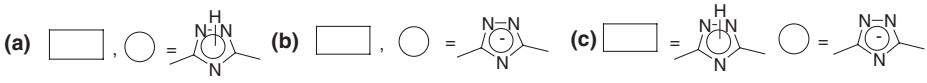
a, X = Cl
b, X = Br



(**126**)



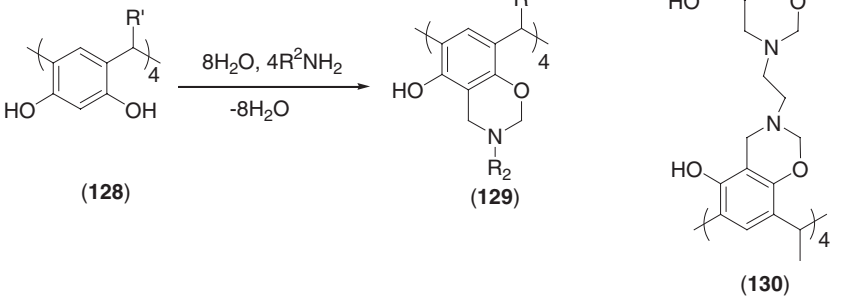
(**127**)



As in the case of tetranuclear systems, interconversions of both dications **126a** and **127a**; and bis-betaines **126b** and **127b**; and mono-betaines **126c** and **127c** could be carried out through the similar operations in a facile manner. The dicationic mono-betaine **126c**, illustrates an unusual case of anion tautomerism where the NH proton migrates between both 1,2,4-triazole rings within the molecule. ^{1}H-NMR studies provide ample evidence of charge distribution within quadrupolar systems **126b** and **127b**. Their bis-betaine nature is reflected in the shielding effect induced upfield shifts of proton signals. The acidic imidazolium C_2–H observe a deshielding effect in **127a**. The hydrogen bond-driven anion interaction with the dicationic framework of **127a** as observed in dynamic NMR studies may be due to favoured pleated loop-like conformations.

D. Calix[4]benz-1,3-oxazines

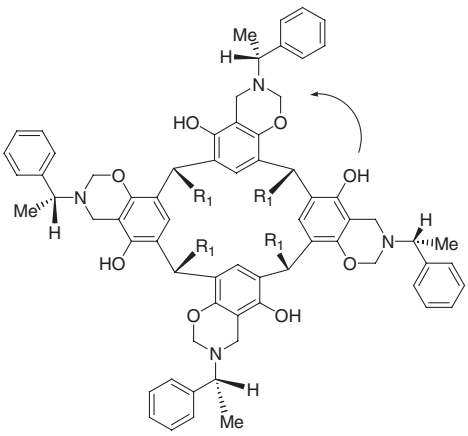
The construction of benz-1,3-oxazine rings on the phenolic units of resorc[4]arene **128** through a Mannich reaction with formaldehyde and a primary amine proceeds strictly in a regiospecific manner to form a racemate of a single regioisomer of calix[4]benz-1,3-oxazine (**129**), where all the newly formed oxazine rings are pointing in the same direction and four intramolecular OH…O hydrogen bonds stabilize the structure (95JA3286). Among functionalized amines, the amino alcohols in some cases provide corresponding **129** but in others, appendages with terminal oxazolidines, the oxazinane moiety is generated (2000EJO3937). Ethylenediamine and formaldehyde react with resorc[4]arene to form an octabenz-1,3-oxazine dimer **130** in which two molecules of the heterocalixarene are connected by four bridges (98TL8833). However, α,ω-diamines generate additional intramolecular bridges between adjacent or opposite oxazine rings (98JA4319).



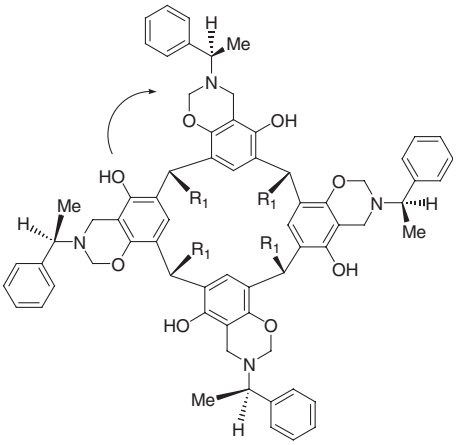
(**128**) (**129**) (**130**)

For investigating diastereoselectivity, Mannich reactions of calix[4]resorcinarene with chiral primary amines were studied (95TL4905, 95TL6221). In a representative case of the reaction of *R*-(+)-1-phenethylamine, formation of two diastereomers **131** and **132** is possible but only one of these is formed with high stereoselectivity as shown by ^{1}H- and ^{13}C-NMR spectra and X-ray confirmed structure **131** with

anti-clockwise helicity and hydrogen bonding (95TL4905). *S*-(+)-1-phenethylamine formed the product with opposite optical rotation. It has been argued that for such a highly diastereoselective process H-bonding of one of the phenolic residues to the first formed oxazine residue as well as steric gearing by chiral auxiliary lead to the chiral cone structure of the product. In an elegant use of heterocyclic conversion in organic synthesis, Heaney and co-workers developed an unprecedented practicable entry for axially chiral enantiomerically pure resorc[4]arene from diastereomerically pure calix[4]benz-1,3-oxazine (99JA6751).



(**131**)



(**132**)

In the presence of even traces of an acid, these optically active heterocalixarenes undergo epimerization, which can be monitored by ^{1}H-NMR or optical rotation. The Mannich reaction of tetramethylresorc[4]arene with *R*-(+)- or *S*-(−)-1-phenethylamine, formed a 4:1 mixture of two diastereomers (98TA4289), from which a single diastereomer could be formed through a Lewis acid-induced oxazine ring opening followed by methoxide assisted diastereomeric ring closure of the oxazine ring. The above investigations provide a variety of calix[4]benz-1,3-oxazine-based chiral hosts, the enantiomeric resolution of which has also been attained (99TL5927).

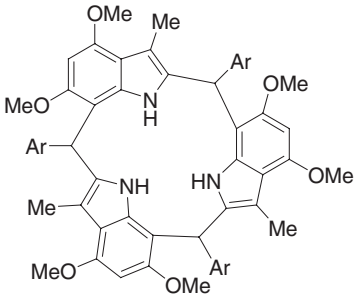
VII. Calix[*n*]indoles and Calix[*n*]benzofurans

A. General

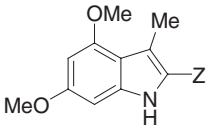
Like monoheteroatomic five-membered aromatic heterocycles with inbuilt 2,5 disposed electron-rich sites, indoles and benzofurans having 2,7 positions activated towards electrophiles such as carbonyl compounds, constitute precursors for performing direct syntheses of calix[*n*]indoles and calix[*n*]benzofurans. These heterocalixarenes provide aromatic π-electron-rich cavities.

B. Calix[*n*]indoles

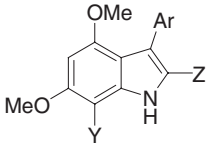
The reactions of 4,6-dimethoxy-3-methylindole (**134**) with aryl aldehydes in the presence of phosphoryl chloride as well as direct reactions of di(4,6-dimethoxy-3-methylindol-2-yl)phenylmethanes with phosphoryl chloride form symmetrically 2,7; 2,7; 2,7 linked calix[3]indoles (**133**) in good yields (89JCS(CC)425, 96AJC311). Alternately, 2-hydroxybenzyl derivatives (**136**) of 4,6-dimethoxy-3-methylindole were made by borohydride reduction of the 2-aroyl derivatives **135** (obtained, in turn, by Vilsmeier reaction on **134**). **136** on treatment with phosphoryl chloride formed **133**. The X-ray crystal structure of calix[3]indole **133** (Ar = C_6H_5) showed two phenyl groups on one side of the mean plane of the macrocycle and one phenyl group on the other side (89JCS(CC)425), whereas **133** (Ar = *p*-BrC_6H_4) revealed a flattened partial cone conformation having three indole NH moieties in up, down and flat orientations with respect to the mean plane of the macrocycle (96AJC311).



(**133**)



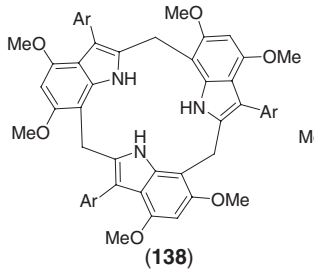
(**134**) Z = H
(**135**) Z = COAr
(**136**) Z = CH(OH)Ar



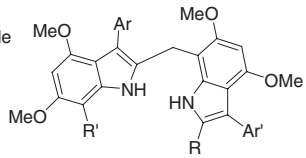
(**137**)

a Z = CHO, Y = H
b Z = CH_2OH, Y = H
c Z = H, Y = CHO
d Z = H, Y = CH_2OH
e Z, Y = CHO
f Z, Y = CH_2OH
g Z, Y = H

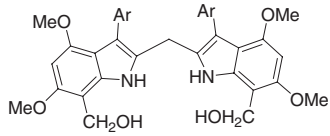
For synthesizing calix[3]indoles **138** having unsubstituted methylene bridges, the alcohols **137b**, **137d** and **137f** were obtained by borohydride reduction of their respective aldehydes formed in turn by controlled Vilsmeier formylation of 3-aryl-4,6-dimethoxyindole (93JCS(CC)819). Both **137b** and **137d** individually undergo acid-catalysed macrocyclization to form calix[3]indoles **138**. Likewise, 2,7-dihydroxy compound **137f** could be condensed with diindolylmethane **139** to form the corresponding **138**. The dialcohol **140** (Ar, Ar′ = *p*-$MeOC_6H_4$), formed from **139** by bisformylation followed by reduction, on condensation with **137g** also formed the corresponding **138**. These synthetic routes (93JCS(CC)819) can enable incorporation of similar or different indoles into the target 2,7 linked calix[3]indoles. It may be noticed that alternate unsymmetrical regiochemistry expected from 2,2′ and 7,7′ condensation modes was not observed. The dialcohol **142** formed by coupling of **137c** with formaldehyde followed by borohydride reduction, on condensation with **137g** gave unsymmetrically 2,2; 7,2; 7,7-linked calix[3]indole **143** along with some linear oligomers (93JCS(CC)819).



(**138**)

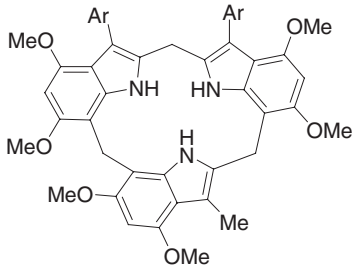


(**139**) R, R' = H
(**140**) R, R' = CH_2OH
(**141**) R = H, R' = CH_2OH

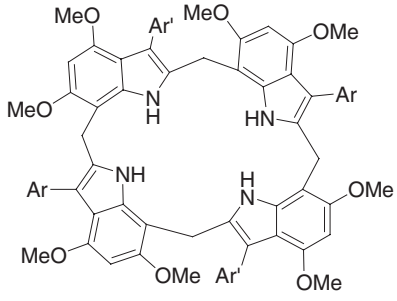


(**142**)

In a careful work-up of the acid-catalysed reactions of 7-hydroxymethyl indoles **137d** (Ar = *p*-Br/Cl/F-C_6H_4), the corresponding symmetrical calix[4]indoles **144** (Ar, Ar′ = *p*-Br/Cl/F-C_6H_4) are also obtained in about 25% yields (95TL8075). Alternatively, calix[4]indoles could be prepared by the acid-catalysed dimerization of the hydroxymethyl dimeric compounds **141** achieved by reduction of related aldehydes, in turn obtained by the selective formylation of 2′,7′-diindolylmethane. This longer route allows the synthesis of calix[4]indoles with two different C_3-aryl substituents. The X-ray structure of **144** (Ar, Ar′ = *p*-BrC_6H_4) reveals a 1,3- alternate conformation (Figure 17). It constitutes a cubic cavity and two associated toluene molecules lie outside the cavity (95TL8075).



(**143**)



(**144**)

In their ^{1}H-NMR spectra, calix[3]indoles **138** and **143** reveal a methylene singlet resonance consistent with a rapidly inverting cone conformer or a fluxional flattened

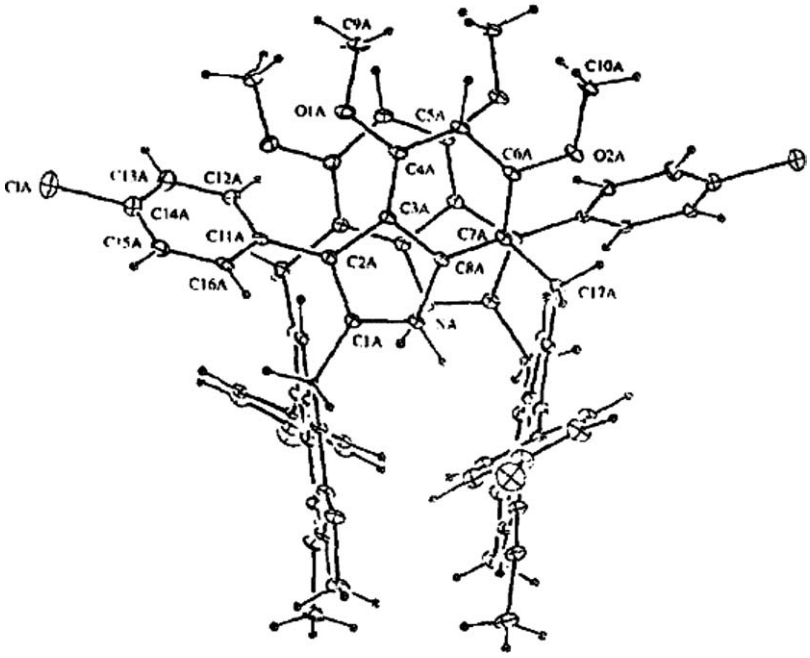
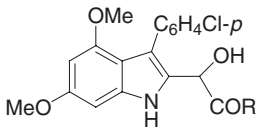


Figure 17. X-ray structure of **144** (Ar, Ar′ = *p*-BrC_6H_4). (Reprinted with permission from 95TL8075, Copyright 1995, Elsevier.)

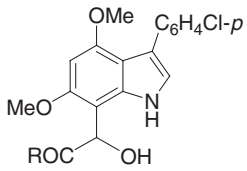
partial cone conformer. The latter being more probable because the related triaryl substituted systems show a flattened partial cone conformation. In contrast to calix-[3]indoles, calix[4]indoles **144** having methylene bridges, in their ^{1}H-NMR spectra show an AB splitting pattern for the methylene protons depicting their non-equivalence due to the rigidity of their structures as compared with the former (95TL8075).

For achieving cone conformations in predominantly flattened partial cone (fpc) calix[3]indoles **133** and **138**, their organization through hydrogen bonding by having amidomethine bridges in place of methylene or arylmethine ones, was investigated (96TL241, 2000T8513). The precursors 2- and 7-hydroxyethanamides **145**–**147**, having primary, secondry and tertiary amide groups were obtained from the corresponding indoles through a sequence of reactions with oxalyl chloride, amines and borohydride (96T8925).

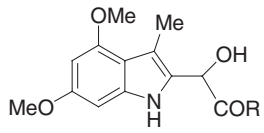


(**145**)

R = (a) NHMe, (b) NH-Bu^n, (c) NH-Bu^t, (d) NH_2, (e) NMe_2, (f) Pyrrolidine



(**146**)

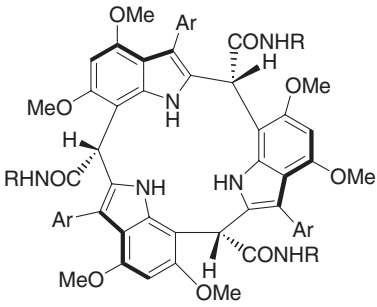


(**147**)

R = (a) pyrrolidine
(b) NH-Bu^t

In the reaction of **145a** with concentrated HCl, solvents influenced the structure of the product calix[3]indole **148**. In THF, a flattened partial cone conformation of **148** predominated, whereas its cone conformer was the major product in CCl_4. In toluene, additional formation of calix[4]indole was also noticed. However, attempts to isolate and fully characterize the cone isomer failed, due to its poor solubility and incompatibility with chromatographic media. Similar reaction of **146a** in THF formed flattened partial cone (fpc) and cone conformers as well as tetra and pentameric products. The solvent effect could be due to its influence on the reactivity of the intermediate cabocation and also on the degree of H-bonding between the indole NH and amide carbonyl O atom. Even the longer chain in **145b**, known to promote formation of cone isomers in calixresorcinarenes (90JA2807), was not of much consequence in forming **148** (2000T8513).

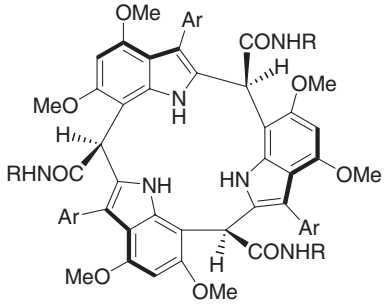
Using a bulkier R suppressed inversion in **148**. Such derivatives prefer to exist as the triaxial isomer putting three amide groups in sterically less demanding positions and invoking H-bonding with indole NH. Thus in the reaction of **145c** with HCl in chloroform, **148** and **149** (R = Bu^t) were separated by chromatography and **148** was crystallized from ethanol. With methoxide, **148** (R = Bu^t) isomerizes irreversibly to thermodynamically more stable **149**, presumably through a carbanion intermediate from deprotonation of a methine group. On reaction with HCl, **146c** formed respective **148** and **149** along with traces of unsymmetrical tetramer. The primary amidoalcohols **145d** and **146d** do not react smoothly with acid and tertiary amidoalcohols **145e**, **145f**, **146e** and **146f** are less reactive and their indole N-methyl derivatives fail to react.



Ar = C_6H_4-Cl-*p*

tri-axial cone

(**148**)



Ar = C_6H_4-Cl-*p*

tri-equatorial fpc

(**149**)

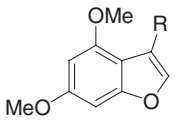
In the X-ray structure of **148 · EtOH** (R = Bu^t), all three *t*-butylamido substituents are in a triaxial arrangement but their bulkiness does not allow all the three amide carbonyls to point simultaneously to the centre of the annulus. Only two COs point to the annulus and are H-bonded with an indole NH. The third CO points away and is not capable of H-bonding. However, all three indole molecules are H-bonded in

someway. The unsymmetrical nature of the three amido groups in the X-ray crystal structure is not reflected in ^{1}H-NMR as in solution, amide groups could be in fluxional equilibrium. An EtOH molecule is placed inside the cavity where its alkyl portion interacts with the electron-rich cup: the oxygen of EtOH hydrogen bonds to an amide NH with the H of the hydroxyl group hydrogen bonds to the methoxy O atom.

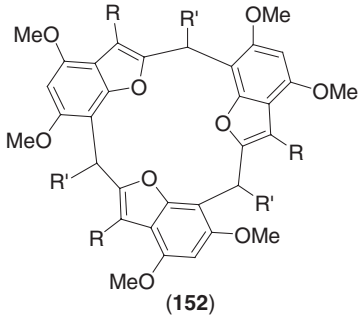
In 3-methylcalix[3]indoles, the absence of steric hindrance around the 3-aryl ring of **148** and **149**, could enhance the formation of a cone conformation. The reaction of **147a** with concentrated HCl gave the fpc and cone products in the ratio 55:45 but **147b** gave only the fpc product. In a single pot mode, involving *in situ* generation of **147a**, the cone conformer was the major product whereas in the case of **145f**, the cone product was formed in trace amounts. The striking difference in product distribution brought about by solvent change is much more pronounced in the case of 3-methyl derivatives. Though the size of the group at position 3 considerably enhances the formation of a cone isomer, so far no substrate or reaction condition has been found to afford only the cone isomer in the case of calix[3]indoles. With relatively limited success in triggering a cone conformation in calix[3]indoles through intramolecular interactions of indole NH and amide CO appended at a methylene linker, Black et al. made some attempts to generate the same by capping the system (2001T2203).

C. Calix[*n*]benzofurans

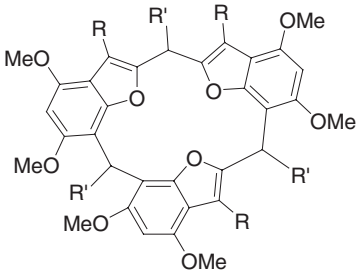
3-Aryl-4,6-dimethoxybenzofuran (**150**), an ambident nucleophile, in contrast to its indole analogue, which undergoes an uncontrolled reaction with formaldehyde and acid [89CC425], reacts smoothly with formaldehyde to afford both symmetrically linked 2,7:2,7:2,7- and unsymmetrically linked 2,2:7,7:2,7- calix[3]-benzofurans **152** and **153** (R = Ar, R′ = H) in moderate yields (99T4803). However, **151** with formaldehyde formed calix[4]benzofuran derivative **154** (R = Bu^t, R′ = H) but with dimethoxymethane and acetic acid afforded the corresponding **152** and **153**.



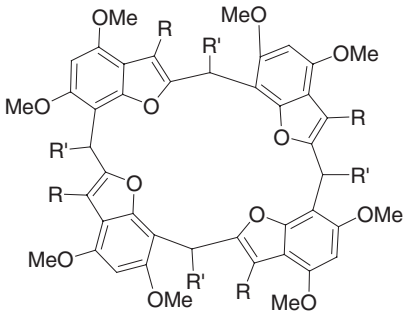
(**150**) R = Ar
(**151**) R = Bu^t



(**152**)

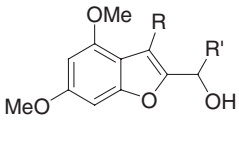


(153)

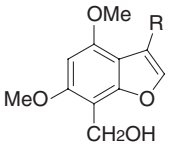


(154)

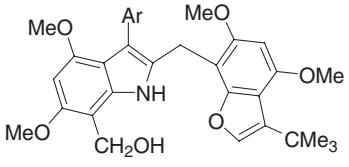
Aryl aldehydes and **150** in the presence of phosphoryl chloride gave both calix[3]indole derivatives which have distinctly different ^{1}H-NMR patterns. The unsymmetrically linked isomer **153** (R′ = Ar) was the major one, probably due to higher reactivity of position 2 over 7. However, **151** reacts with benzaldehyde to give only a symmetrically linked product **152** (R′ = Ar) as in this case the steric hindrance at position 2 of **151** causes the reaction to proceed at position 7. In case of **155** (R = C_6H_5, R′ = *p*-MeC_6H_4 and R = *p*-BrC_6H_4, R′ = C_6H_5), conformers related to the axial and equatorial nature of the methine aryl group could be separated. The X-ray structure of symmetrical trimer **152** (R = C_6H_5, R′ = *p*-MeC_6H_4) showed its flattened partial cone conformation (99T4803).



(155)

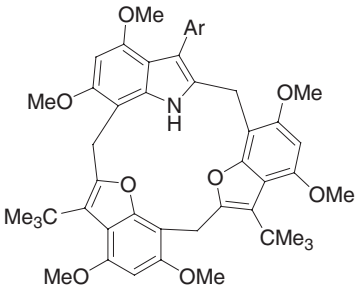


(156)

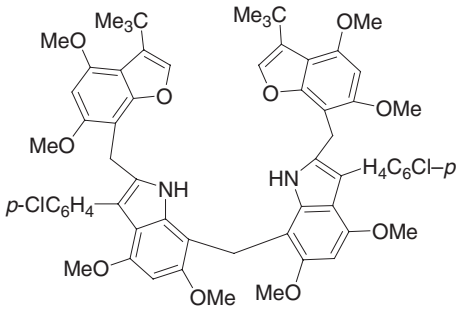


(157)

In an alternate approach (2002T5125), 2-hydroxymethylbenzofurans **155** (R = C_6H_5, R′ = H and R = Bu^t, R′ = H), on treatment with K-10 clay gave the corresponding unsymmetrically linked calix[3]benzofurans **153** as major products whereas acid-catalysed reactions of **156** (R = C_6H_5, R′ = H and R = Bu^t, R′ = H) afforded only the corresponding symmetrically linked derivatives **152**. Acid-catalysed reactions of secondary alcohols **155** (R = C_6H_5, R′ = *p*-MeC_6H_4, *p*-ClC_6H_4, Me, CONH-Bu^t, $CONH_2$, CONHMe, COOMe) gave the corresponding symmetrically oriented **152** only. In the case of **155** (R = C_6H_5, R′ = *p*-ClC_6H_4), the corresponding calix[4]benzofuran **154** was also isolated. Of the two configurational isomers of **152** (R = C_6H_5, R′ = CONH-Bu^t), the one which crystallized, revealed in its X-ray structure (2002T5125) a flattened partial cone configuration with the three *tert*-butylcarboxamido groups oriented in one equatorial and two axial positions. Its ^{1}H-NMR shows its equilibrium with a cone conformation which could not be isolated.

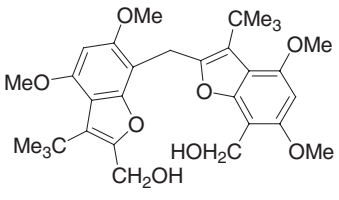


(**158**)

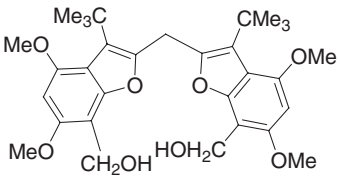


(**159**)

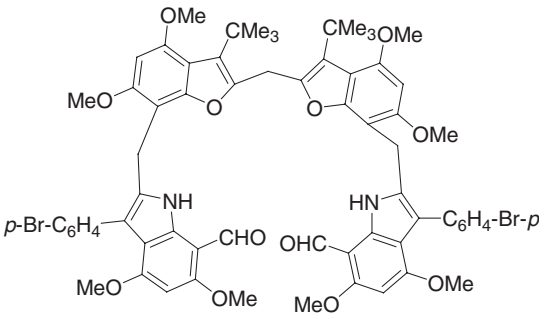
Montmoroltonitrile K-10 clay treatment of alcohol **157**, obtained by acid-catalysed reaction of 7-hydroxymethylbenzofuran and indole-7-carbaldehyde derivatives and subsequent reduction, surprisingly formed the symmetrically linked 2,7; 2,7; 2,7; calix[1]indole[2]benzofuran (**158**) having two benzofuran moieties. The initially formed linear tetramer **159** also similarly afforded **158** (2002JCS(CC)810). Since acid-catalysed reaction of 3-Bu^t-4,6-dimethoxy-7-hydroxymethylbenzofuran and 3-(*p*-bromophenyl)-7-hydroxymethyl-4,6-dimethoxyindole afforded the corresponding calix[3]benzofuran derivative and **158**, it has been argued that in the above sequence the first formed **159** cleaves to parent heterocyclic units which recombine to form **158**. It has also been obtained from reaction of 3-(4′-bromophenyl)-4,6-dimethoxyindole with dialcohol **160** conveniently formed from the corresponding 2- and 7-benzofurancarbaldehydes and formaldehyde and subsequent reduction. When crystallized from a dichloromethane and ethyl acetate mixture, **158** forms a 1:1 complex with dichloromethane and its X-ray structure revealed a flattened partial cone structure.



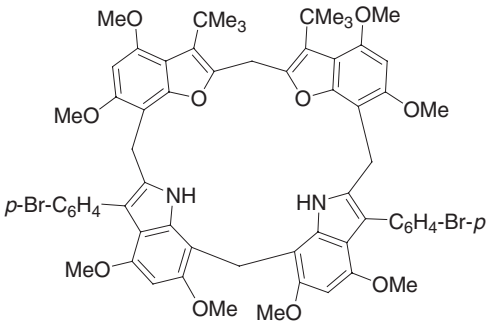
(**160**)



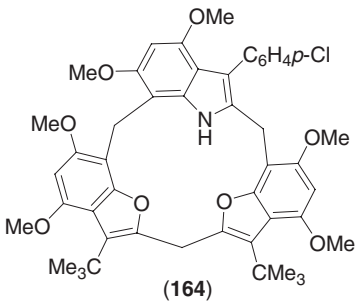
(**161**)



(**162**)



(**163**)



(**164**)

The diol **161**, obtained by condensation of appropriate benzofuranaldehyde with formaldehyde and subsequent reduction, on reaction with 4′-bromophenyl-4,6-dimethoxyindole-7-carbaldehyde gave the tetrameric dialdehyde **162**. The alcohol derived from **162** on dry-HCl-induced macrocyclization gave **163** along with an unsymmetrically linked heterocalix[3]arene **164**, which as such was also formed in good yields from **161** and 3-(*p*-bromophenyl)-4,6- dimethoxyindole in the presence of clay. The X-ray structure of **164** reveals its flattened partial cone configuration and **164** forms a stable Cu(I) complex whereas isomeric **158** fails to do so (2002JCS(CC)810). These hybrid heterocalixarenes synthesized in high-yielding reactions represent unprecedented systems suitable for development of new and exciting molecular receptors.

VIII. Cyclic Urea-Based Heterocalixarenes

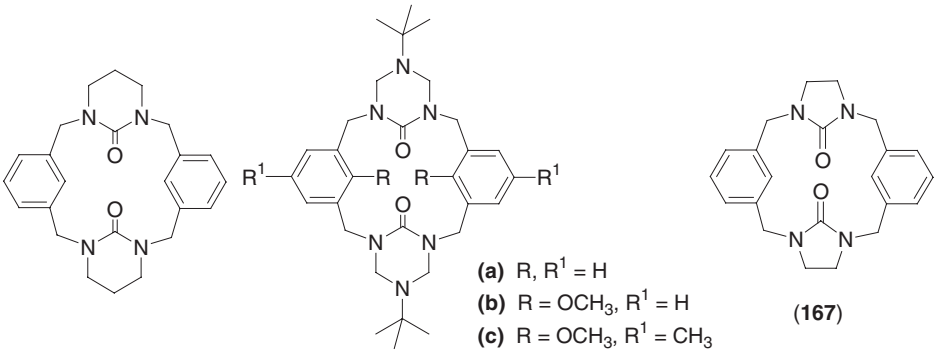
A. General

The biologically ubiquitous urea unit when embedded in the aromatic or non-aromatic heterocyclic component of a heterocalixarene has an intrinsic resonating character revealing structures which generate possibilities of varied interacting capability and conformations. The urea oxygen is known to be sterically less hindered and a stronger binding site than an ether oxygen (84JA7150). The limited number of such heterocalixarenes reported so far elaborate unique binding and conformational characters.

B. Perhydro Cyclic Urea-Based Heterocalixarenes

The urea unit in the cyclic urea component of these heterocalixarenes is capped with $–(CH_2)_2–$, $–(CH_2)_3–$ and $–CH_2–N(Bu^t)–CH_2–$ moieties. In a straightforward synthetic approach, the bisanions of cyclic ureas, tetrahydropyrimidin-2-one (88JCS(P1)13), 5-*t*-butyltetrahydro-1,3,5-triazin-2-one (92TL1021, 95JOC6946) and imidazolidin-2-one (92TL1021) on reaction with 1,3-*bis*(bromomethyl)benzene

or its appropriate derivatives provide heterocalixarenes **165**, **166** and **167** in relatively low yields.



(**165**) (**166**) (**167**)

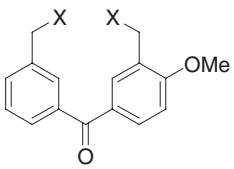
In its variable temperature NMR studies, compound **165** revealed cone and 1,3-alternate structures (88JCS(P1)13). For compound **167**, ^{1}H- and ^{13}C-NMR studies (95JOC6946) point to its flattened partial cone conformation with two equally populated *syn* and *anti* conformers in equilibrium. The X-ray structures of **166a–c** again reveal their flattened partial cone conformations (92TL1021). In **166a**, the two aromatic rings are approximately parallel but the triazinone rings though essentially parallel to the cone axis have the urea carbonyls pointing in opposite directions. However, in **166b** and **166c**, the urea carbonyls in parallel triazinone units point in the same direction. The aromatic rings occupy perpendicular planes with the methoxy group of the flattened ring facing a π-cloud of the second ring exhibiting a C–H…π interaction and the other OCH_3 points in the opposite direction to the triazinone carbonyl. The methoxy groups experiencing π-interaction appear upfield in the ^{1}H-NMR spectra. The low-temperature ^{1}H-NMR of **166a** reveals the existence of a conformational equilibrium of *syn* and *anti* forms which is influenced by solvent.

C. Conjugated Cyclic Urea-Based Heterocalixarenes

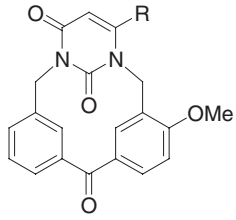
Uracil, benzimidazol-2-one, and quinazolin-2,4-dione units constitute sub-cycles of these heterocalixarenes where, unlike the first category, the urea moiety is extensively conjugated. This category represents both odd- and even-membered heterocalixarenes having varied combinations of cyclic ureas and arenes and also of methylene and carbonyl bridges.

Trimeric heterocalixarenes **170**, **171** and **172** characterized by one cyclic urea, two arenes and a carbonyl bridge have been obtained by TBA · HSO_4 catalysed condensations of uracils, benzimidazolin-2-ones and quinazolin-2,4-dione with the dibromide **169** formed by *N*-bromosuceinamide bromination of benzophenone derivative **168**, in turn obtained by Friedel–Crafts aroylation of 2-methylanisole with

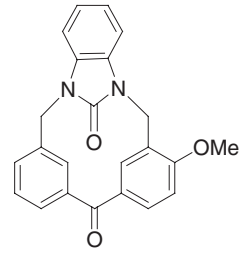
3-methylbenzoyl chloride (2000JCS(P1)2295). In case of the uracil-based systems, of the two possibilities **170** and **173**, structures **170** have been confirmed by NOE (nuclear overhauser effect) studies and single crystal X-ray analysis. However, structure **172** in the case of the quinazolin-2,4-dione based system, has been assigned by analogy only.



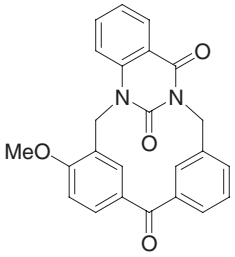
(168) X = H
(169) X = Br



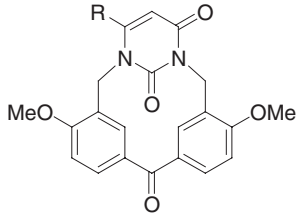
(170) **a**, R = H
b, R = CH_3



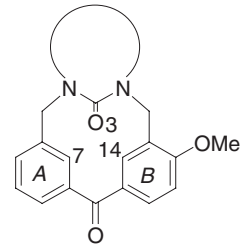
(171) a, Z = H
b, Z = NO_2



(172)



(173)



(174)

Both **170a** and **171a** elaborate similar inwardly flattened partial cone conformations. A collective representation **174** is drawn having common structural features. The heterocyclic rings in both **170a** and **171a** are nearly perpendicular to the mean plane of the bridging carbons and phenylene rings 'A' and 'B' are in anti and gauche positions orientating C-7 H and C-14 H, respectively, above and below the plane. C-7 H shows a unique short intramolecular contact with imide O_3 and C-14 H experiences interaction with the π-cloud of the heterocycle which is stronger in the case of **171a** than in **170a**. In their ^{1}H-NMR, due to these interactions, signals due to C-7 H and C-14 H are shifted upfield. Compound **171a** crystallizes as **171a** $\cdot$ $(H_2O)_{0.5}$ and shows a unique array of H-bonds in which three of the four CH of benzimidazol-2-one and the imide O, carbonyl O and water molecules are involved. Each water molecule is strongly H-bonded to four molecules of **171a** (Figure 18) and is responsible for engineering the crystal which crumbles in its absence. In the packing of **171a**, face to face $\pi-\pi$ interactions of rings '*B*' of two molecules are observed and $\pi-\pi$ stacking of benzimidazolones is not visible (2000JCS(P1)2295).

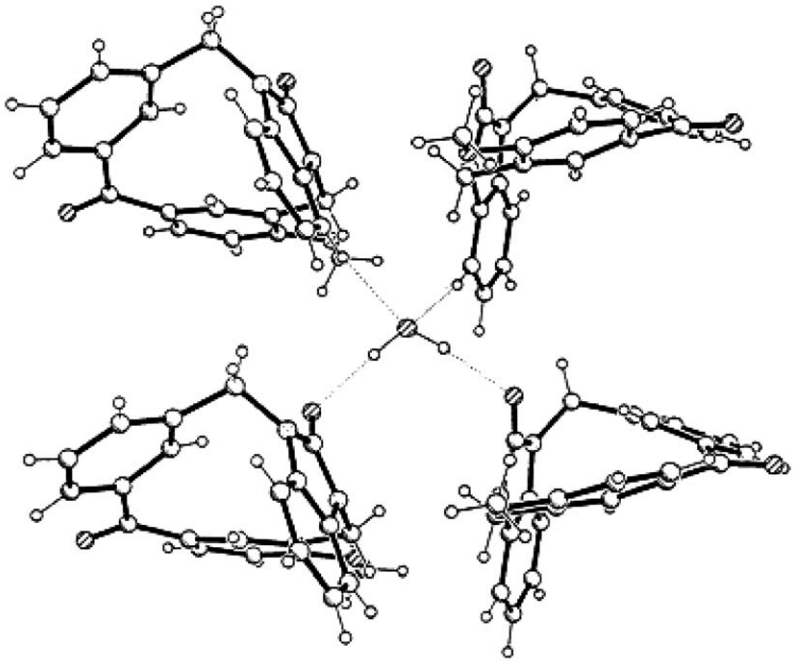


Figure 18. X-ray structure showing four molecules of **171a** placed in tetrahedral geometry around a water molecule. (Reprinted with permission from 2000JCS(P1)2295, Copyright 2000, Royal Society of Chemistry.)

Tetrameric calix[2]uracil[2]arenes **176**, having similar or different substitution profiles in both arenes, have been obtained by PTC catalysed condensations of 1,3-*bis*(bromomethyl) benzene derivatives with 1,3-*bis*[(1-uracilyl)methyl]benzene derivatives **175** obtained in turn by selective *N*-1 alkylation of 2,4-*bis*(trimethylsilyloxy)-pyrimidine with 1,3-*bis*(bromomethyl)benzene derivatives (97TL3607, 99JOC7717). X-ray, variable temperature ^{1}H-NMR and molecular modelling studies show that these heterocalixarenes, depending on the nature of the substituents on position 2 of the 1,3-phenylene rings attain an inward flattened partial cone, a cone or other flexible structures.

The X-ray structure of **176g** shows an inward flattened partial cone conformation where the OAc of the flattened ring faces the π-cloud of the second phenylene ring and experiences a C–H…π interaction. In the 2:1 complex of **176j** with ethanol, two crystallographically independent molecules (Figure 19) in the unit cell reveal a cone conformation and are bound with ethanol in an unusual 3-centred H-bonding at H of OH and CH_2 with the C4$=$O of a uracil of one molecule and at O of OH with the C-5 H of uracil of second molecule. Its crystal packing displays extensive $\pi-\pi$ interactions between various rings. The compound **176j** also forms crystalline complexes with methanol and ethylene glycol, loss of which turns crystals to amorphous powders, indicating H-bonded engineering of these crystals.

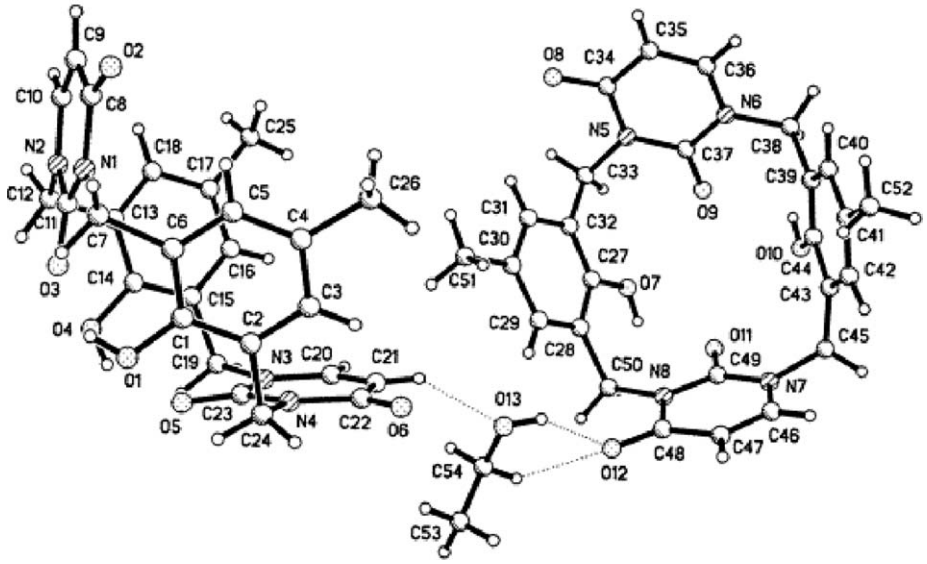
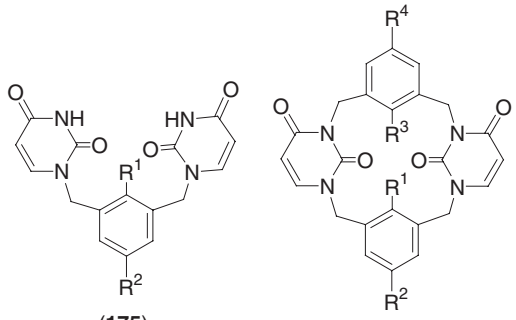


Figure 19. X-ray crystal structure of **176j**·$(EtOH)_{0.5}$. (Reprinted with permission from 99JOC7717, Copyright 1999, American Chemical Society.)

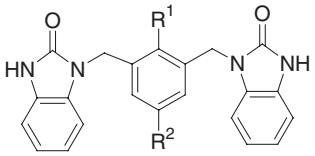


	R^1	R^2	R^3	R^4
(a)	H	H	H	H
(b)	OMe	Me	H	H
(c)	H	H	OMe	Me
(d)	OMe	Me	OMe	Me
(e)	OMe	Me	OAc	Me
(f)	OAc	Me	OMe	Me
(g)	OAc	Me	OAc	Me
(h)	OAc	t-Bu	OAc	t-Bu
(i)	OAc	H	OAc	H
(j)	OH	Me	OH	Me
(k)	OH	Me	OH	NO_2

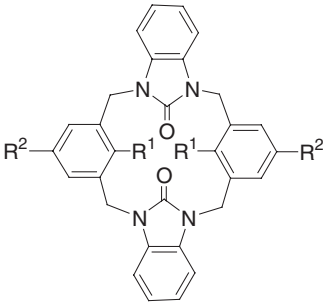
In the ^{1}H-NMR spectrum of **176g**, a bridged CH_2 shows two AB quartets and one OAc appears upfield. Similar profiles of ^{1}H-NMR spectra reveal inward flattened partial cone conformations in solution for all **176** having OAc or OMe at C-2 of phenylene attached at *N*-1, *N*-1 of uracil. But **176a**, **176c** and **176j** which have H or OH at this site and show broad signals for $–CH_2–$, have flexible structures in solution. However, their variable temperature ^{1}H-NMR studies show the existence of two or more conformers which equilibrate at room temperature.

Tetrameric calix[2]benzimidazolone[2]arenes **178a** and **178b** and octameric calix[4]benzimidazolone[4] arenes **179a**–**f**, have been formed by high dilution and template induced condensation of 1,3-*bis*(bromomethyl)benzene and the trinuclear

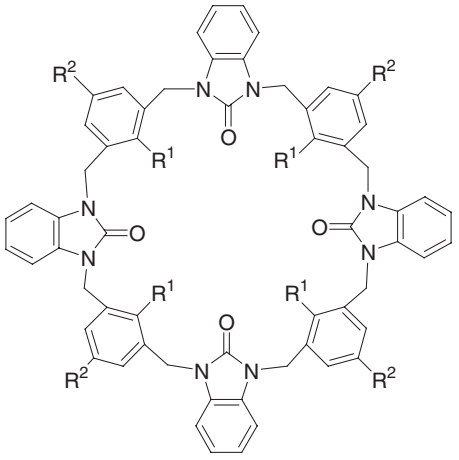
system **177** formed by condensation of *N*-propen-2-ylbenzimidazolone and 1,3-*bis*(bromomethyl)-benzene followed by deprotection (96JCS(P2)2359). The compounds **176e** and **176f** were obtained by BBr_3 mediated cleavage of **176a** and **176b**. Some of these heterocalixarenes reveal unique molecular shapes and interactions in X-ray structures of their complexes with solvent molecules.



(**177**)



(**178**)



(**179**)

(a) R^1 = OMe, R^2 = H; (b) R^1 = OMe, R^2 = Bu^t; (c) R^1 = OMe, R^2 = Ph; (d) R^1 = OMe, R^2 = OMe; (e) R^1 = OH, R^2 = H; (f) R^1 = OH, R^2 = Bu^t

In the **179a** · $(CH_2Cl_2)_2$ complex, the heterocalixarene adopts an ellipsoidal shape with methoxy and carbonyl oxygen atoms pointing away from the cavity and the guest molecule lies partially inside the host but its disorder and high thermal motion does not allow a concise description of host–guest interactions. In the **179b** · (toluene)$_2$(water) complex, **179b** has a spherical shape and its closed cavity completely encapsulates one toluene molecule (Figure 20) and the second toluene molecule is located in channels between molecules. The **179c** · (acetone)(dichloromethane) complex reveals a mostly elliptical molecular shape (Figure 21) for the host which completely encloses the guest acetone through an electrostatic fit. The guest dichloromethane is placed outside the cavity near the rim of the molecule. The host molecules **179a**–**c** in their complexes reveal packing such that a benzimidazolone unit faces another symmetry centred related mate. In the **179f** · (toluene)$_3$ complex, the host molecule creates two anti-parallel partial cone cavities thus adopting a huge chair conformation (Figure 22) supported by H-bonds. In this complex, solvent molecules occupy both intramolecular cavities and intermolecular voids of the crystal lattice (96JCS(P2)2359).

The tetrameric systems **181** and **182** marked for having two carbonyl bridges, one cyclic urea and three arenes or two arenes and one pyridine nuclei have been

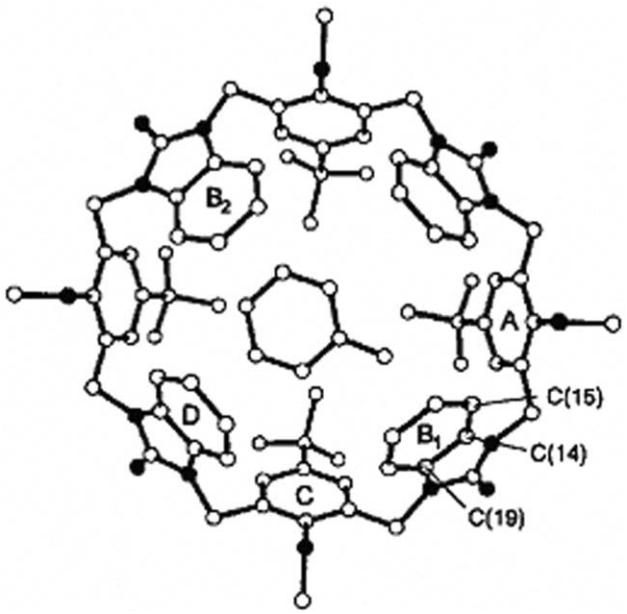


Figure 20. X-ray structure of **179b** · (toluene)$_2$(water) showing incapsulation of one toluene molecule. (Reprinted with permission from 96JCS(P2)2359, Copyright 1996, Royal Society of Chemistry.)

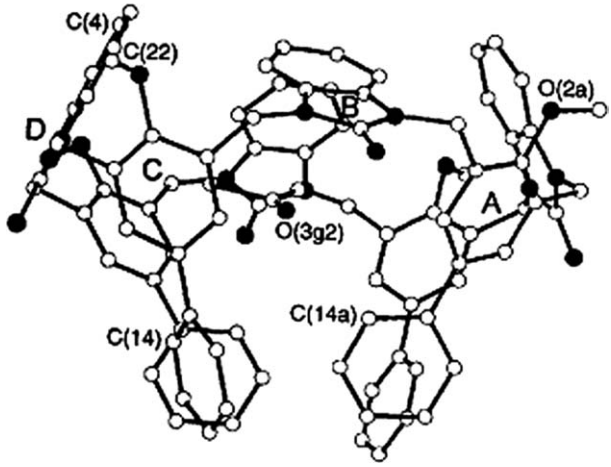


Figure 21. Elliptical molecular conformation of **179c** from the X-ray structure of the **179c** · (acetone)(dichloromethane) complex. (Reprinted with permission from 96JCS(P2)2359, Copyright 1996, Royal Society of Chemistry.)

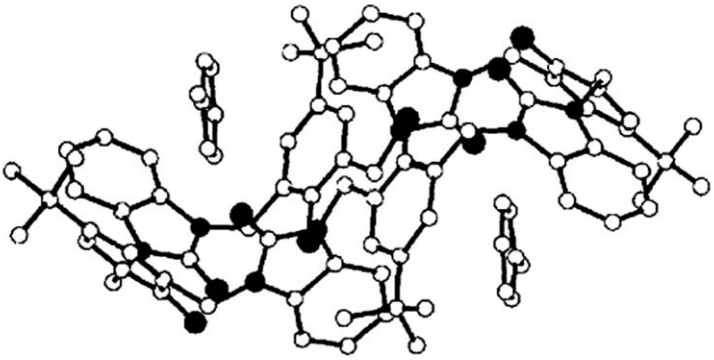
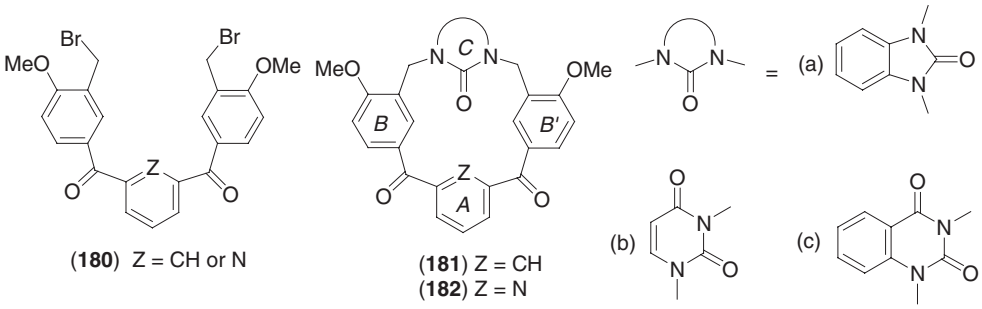


Figure 22. Chair conformation of **179f** from the X-ray structure of **179f** · $(toluene)_3$ complex. (Reprinted with permission from 96JCS(P2)2359, Copyright 1996, Royal Society of Chemistry.)

conveniently synthesized by TBA · HSO_4-catalysed condensation of the respective cyclic urea with trimeric precursor **180** formed, in turn, by (i) Friedel–Crafts aroylation of 2-methylanisole with isophthaloyl chloride or pyridine 2,6-dicarbonyl dichloride and (ii) NBS bromination. Using 4-methylanisole in this sequence of steps, isomeric systems were also formed (2000JCS(P1)1037).



The compound **181a**, on crystallization from chloroform benzene forms an inclusion complex (1:1) with benzene which in its X-ray crystal structure (Figure 23) reveals a partial cone conformation with an isophthaloyl unit placed anti to the rest of the rings and the two methoxyaryl rings are almost perpendicular. The two rings in pairs A,C and B,B′ are placed 7.4 and 6.8 Å apart generating an almost square cavity. The benzene molecule exhibits a face-to-face $\pi-\pi$ interaction with benzimidazole which in turn shows a $\pi-\pi$ interaction with an isophthaloyl ring of a symmetry related molecule. Thus the benzimidazolone ring is sandwiched between benzene and isophthaloyl rings. The imide carbonyl oxygen is H-bonded to a methoxy H and adjacent aryl C–H of ring B whereas the O of the bridging carbonyls are H-bonded to a bridged methylene H. Energy minimization studies on these heterocalixarenes reveal that all of them have, by and large, similar conformations as shown in the X-ray and ^{1}H-NMR studies.

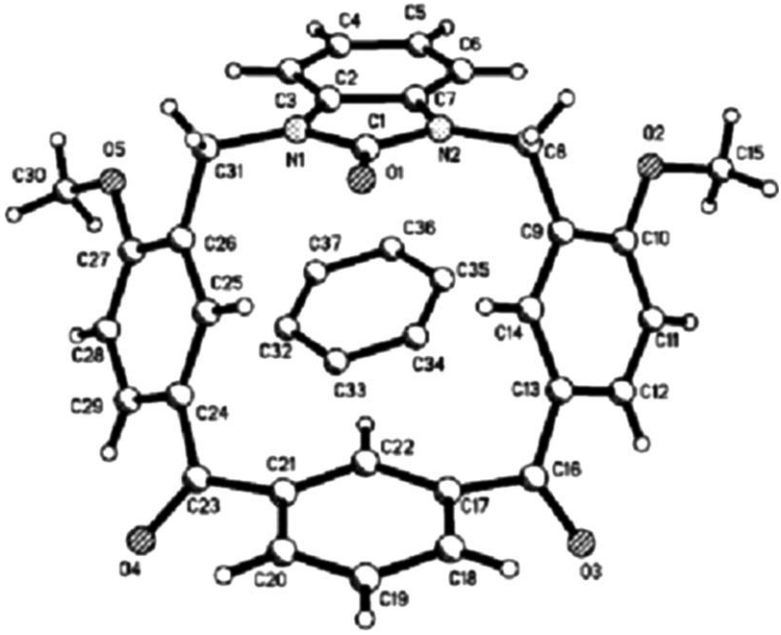
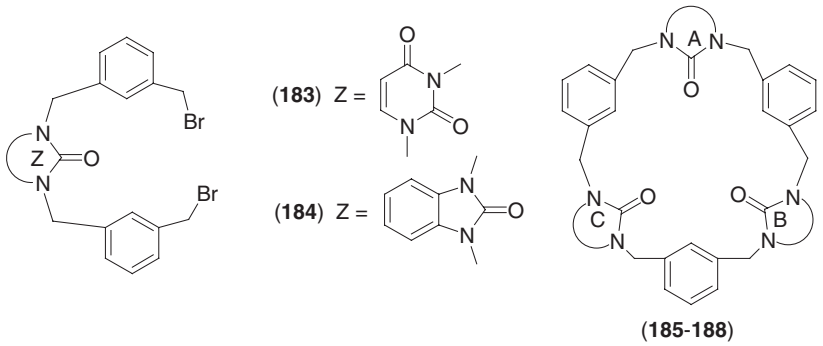


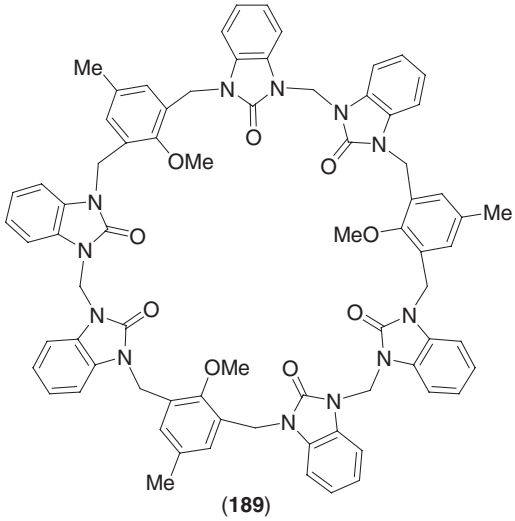
Figure 23. X-ray structure of the **181a** · (benzene) complex. (Reprinted with permission from 2000JCS(P1)1037, Copyright 2000, Royal Society of Chemistry.)

The ^{1}H-NMR splitting patterns of methylene signals of these heterocalixarenes reveal their variable flexibility depending on the nature of the cyclic ureas and on moving from benzimidazolone to uracil to quinazolone the rigidity of respective calixarenes increases (2000JCS(P1)1037).

Based on the rational of binding modes of 18-crown-6, heterocalixarenes **185**–**188** were designed for RNH_3^+/K^+ binding selectivity. Their synthesis involved a straightforward condensation of respective trinuclear systems **175** and **177** (R^1, $R^2 = H$) with the dibromides **183** and **184**, formed from the corresponding cyclic urea and 1,3-*bis*(bromomethyl)benzene (2000MI2).



(185-188)



(**189**)

(**185**) A, B, C =

(**186**) A, B = C =

(**187**) A, B = C =

(**188**) A,B,C =

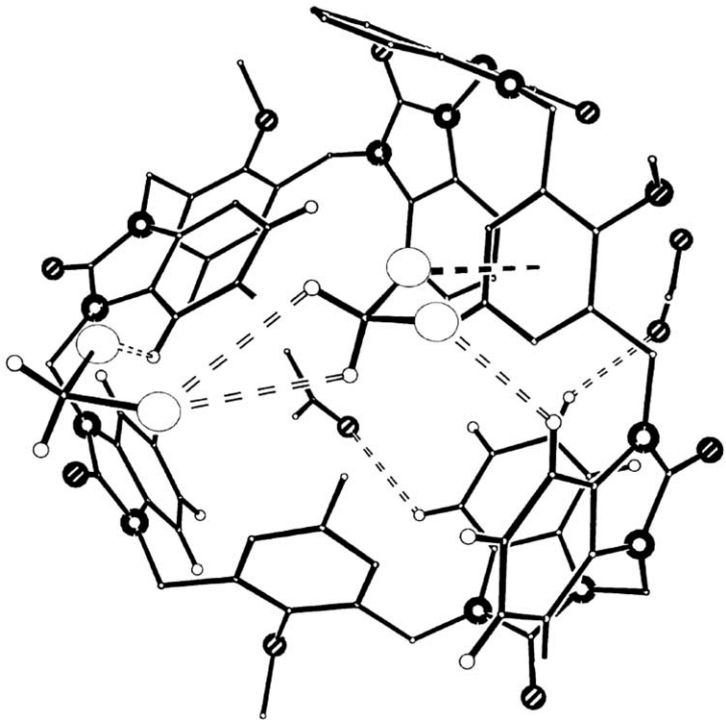


Figure 24. X-ray structure of the **189** · (acetone)$_2$(dichloromethane)$_2$ complex. (Reprinted with permission from 96JCS(P2)2359, copyright 1996, Royal Society of Chemistry.)

Energy minimization of these heterocalixarenes shows that two imide carbonyls are directed inwards towards the cavity and the third one is placed outside. But on complexation with an ammonium cation, all three carbonyls are directed inwards and form H-bonds with H_3N^+ – and the complexes are stabilized by -30–$50\,kJ\,mol^{-1}$ in comparison with the parent heterocalixarene. Both in liquid–liquid and liquid–solid extraction studies, these heterocalixarenes selectively extract $H_3N^+Bu^t$ picrate over K^+ picrate and the compound **186** has the highest selectivity (2000M1371).

Weber et al. (97JCS(CC)1461) has synthesized a rare odd-membered larger-sized (C9) hetero[6]benzimidazolone[3]arene system **189** via a two-step fragment condensation from 2,6-*bis*(bromomethyl)-4-methylanisole and methylene-1,1-*bis*(benzimidazolone) building elements using blocking/deblocking high dilution and template (3 equivalent Cs_2CO_3) techniques as used for synthesizing **179** (96JCS(P2)2359). It crystallized from acetone and dichloromethane (1:4) to form a crystalline complex of 1:2:2 stoichiometric ratio. In its X-ray structure (Figure 24), one acetone molecule held by –C–H…O interaction with an imide carbonyl is included in the cavity. The second acetone molecule, again experiencing a similar interaction, is bound on the perimeter. The two dichloromethane guests are located on the host molecular surface and experience –C–H…Cl interactions to each other and to the host in a consecutive manner. The cascade ends in a Cl…π interaction with the anisole ring. The side-on-side stacking of symmetry center-related host molecules with respect to the benzimidazolone plane appears repeatedly and hetero-units stacking constitutes an important motif contributing to crystal formation.

IX. Conclusions

Like a jewel in a ring, a heteroatom can provide physicochemical value in a heterocycle (97MI1). Similarly, replacing phenolic unit(s) in the structural core of calixarenes by heterocyclic unit(s)generates similar effect in heterocalixarenes. Of the numerous possible structural designs, except for the oldest heterocalixarene – calix[4]pyrrole, only a few have been synthesized and even fewer have been structurally elaborated and evaluated for their receptor and related characters. In addition to single or multi-step synthetic approaches, their facile procurement by heterocyclic transformations on some easily available heterocalixarenes opens up a unique practicable and pliable mode of forming many otherwise inaccessible inspiring new chemical entities including heterocalixarenes and demands exploration. Conspicuously, conformations of heterocalixarenes are influenced by a variety of intra- and intermolecular non-covalent interactions induced by core and/or appended species and which are quite often responsible for engineering their crystals-supramolecules. Since these phenomena are of prime relevance in understanding supramolecular interactions in biological systems and in the development of new materials, it would be of interest to incorporate biologically significant heterocycles as sub-cycles of heterocalixarenes. Thus, it is left to human imagination as to how many such systems await investigation to develop newer chemical entities of potential use for human welfare.

Acknowledgements

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References

06MI1 W. J. Hale, W. D. McNally, and C. J. Pater, *Am. Chem. J.*, **35**, 72 (1906).
55JOC1147 R. G. Ackman, W. H. Brown, and G. F. Wright, *J. Org. Chem.*, **20**, 1147 (1955).
56CJC1147 W. H. Brown and H. Sawatzky, *Can. J. Chem.*, **34**, 1147 (1956).
56JOC447 R. E. Beals and W. H. Brown, *J. Org. Chem.*, **21**, 447 (1956).
58CJC371 W. H. Brown and W. N. French, *Can. J. Chem.*, **36**, 371 (1958).
58CJC537 W. H. Brown and W. N. French, *Can. J. Chem.*, **36**, 537 (1958).
69TL1493 M. Ahmed and O. Meth-Cohn, *Tetrahedron Lett.*, **10**, 1493 (1969).
71CJC4017 W. H. Brown, B. J. Hutchinson, and M. H. MacKinnon, *Can. J. Chem.*, **49**, 4017 (1971).
72JCS(CC)1059 K. R. Reistad, P. Groth, R. Lie, and K. Undheim, *J. C. S. Chem. Commun.*, 1059 (1972).
73JCS(CC)534 M. Chastrette and F. Chastrette, *J. C. S. Chem. Commun.*, 534 (1973).
73TL4043 Th. Kauffmann and H. -H. Kniese, *Tetrahedron Lett.*, **14**, 4043 (1973).
74MI1 A. I. Meyers, Heterocycles in Organic Synthesis, Wiley-Interscience, New York (1974) 221.
76ICA16 A. J. Rest, S. A. Smith, and I. D. Tyler, *Inorg. Chim. Acta*, **LI**, 16 (1976).
76JA7414 Y. Kobuke, K. Hanji, K. Horiguchi, M. Asada, Y. Nakayama, and J. Furukawa, *J. Am. Chem. Soc.*, **98**, 7414 (1976).
77JINC1449 A. Corsini and J. M. Panoyan, *J. Inorg. Nucl. Chem.*, **39**, 1449 (1977).
77OS74 M. Chastrette, F. Chastrette, and J. Sabadie, *Org. Synth.*, **57**, 74 (1977).
81JCS(CC)149 M. de S. Healy and A. J. Rest, *J. C. S. Chem. Commun.*, 149 (1981).
81JOC4143 P. D. Williams and E. LeGoff, *J. Org. Chem.*, **46**, 4143 (1981).
82JOC4370 H. Hart and Y. Takehira, *J. Org. Chem.*, **47**, 4370 (1982).
84JA7150 D. J. Cram, I. B. Dicker, M. Lauer, C. B. Knobler, and K. N. Trueblood, *J. Am. Chem. Soc.*, **106**, 7150 (1984).
85JCS(P1)973 M. de S. Healy and A. J. Rest, *J. Chem. Soc. Perkin Trans. 1*, 973 (1985).
86JA6074 G. R. Newkome, Y. J. Loo, K. J. Theriot, and F. R. Fronczek, *J. Am. Chem. Soc.*, **108**, 6074 (1986).
87JCS(CC)854 G. R. Newkome, Y. J. Joo, and F. R. Fronczek, *J.C.S. Chem. Commun.*, 854 (1987).
88AGE406 E. Vogel, W. Haas, B. Knipp, J. Lex, and H. Schmickler, *Angew. Chem., Int. Ed.*, **27**, 406 (1988).
88AGE409 W. Haas, B. Knipp, M. Sicken, J. Lex, and E. Vogel, *Angew. Chem. Int. Ed.*, **27**, 409 (1988).
88JCS(P1)13 J. A. E. Pratt and I. O. Sutherland, *J. Chem. Soc. Perkin Trans. 1*, 13 (1988).
89AGE1651 E. Vogel, P. Rohrig, M. Sicken, B. Knipp, A. Herrmann, M. Pohl, H. Schmickler, and J. Lex, *Angew. Chem. Int. Ed.*, **28**, 651 (1989).
89AX(C)137 A. Hazell, *Acta Cryst.*, **C45**, 137 (1989).

89JCS(CC)425 D. St. C. Black, D. C. Craig, and N. Kumar, *J. C. S. Chem. Commun.*, 425 (1889).
90JA2807 Y. Tanaka, Y. Kato, and Y. Aoyama, *J. Am. Chem. Soc.*, **112**, 2807 (1990).
90JOC5714 G. R. Newkome, Y. J. Joo, D. W. Evans, F. R. Fronczek, and G. R. Baker, *J. Org. Chem.*, **55**, 5714 (1990).
91CB233 A. Gast and E. Breitmaier, *Chem. Ber.*, **124**, 233 (1991).
91JHC991 S. Tanaka and H. Tomokuni, *J. Heterocyclic Chem.*, **28**, 991 (1991).
92TL1021 P. R. Dave, G. Doyle, T. Axenrod, H. Yazdekhasti, and H. L. Ammon, *Tetrahedron Lett.*, **33**, 1021 (1992).
93JCS(CC)819 D. St. C. Black, M. C. Bowyer, N. Kumar, and P. S. R. Mitchell, *J. C. S. Chem. Commun.*, 819 (1993).
94JA10775 C. M. Kretz, E. Gallo, E. Solari, C. Floriani, A. Chiesi-Villa, and C. Rizzoli, *J. Am. Chem. Soc.*, **116**, 10775 (1994).
94JCS(P1)2881 R. M. Musau and A. Whiting, *J. Chem. Soc. Perkin Trans. 1*, 2881 (1994).
94T9113 F. H. Kohnke, M. F. Parisi, F. M. Raymo, P. A. O'Neil, and D. J. Williams, *Tetrahedron*, **50**, 9113 (1994).
95AGE661 B. Konig, M. Rodel, P. Bubenitschek, and P. G. Jones, *Angew. Chem. Int. Ed.*, **34**, 661 (1995).
95AGE781 S. Kozhushkov, T. Haumann, R. Boese, B. Knieriem, S. Scheib, P. Bauerle, and A. de Meijere, *Angew. Chem. Int. Ed.*, **34**, 781 (1995).
95JA2793 D. Jacoby, S. Isoz, C. Floriani, A. Chiesi-Villa, and C. Rizzoli, *J. Am. Chem. Soc.*, **117**, 2793 (1995).
95JA3286 R. Arnecke, V. Bohmer, E. F. Paulus, and W. Vogt, *J. Am. Chem. Soc.*, **117**, 3286 (1995).
95JCS(CC)1239 E. Alcalde, M. Alemany, L. Perez-Garcia, and M. L. Rodriguez, *J. C. S. Chem. Commun.*, 1239 (1995).
95JOC6946 P. R. Dave, G. Doyle, T. Axenrod, H. Yazdekhasti, and H. L. Ammon, *J. Org. Chem.*, **80**, 6946 (1995).
95JOC7406 B. Konig, M. Rodel, P. Bubenitschek, P. G. Jones, and I. Thondorf, *J. Org. Chem.*, **60**, 7406 (1995).
95MI1 J. Marie Lehn, Supramolecular Chemistry, VCH, New York (1995).
95TL4905 M. T. El. Gihani, Y. Heaney, and A. M. Z. Slawin, *Tetrahedron Lett.*, **36**, 4905 (1995).
95TL6221 R. Arnecke, V. Bohmer, S. Friebe, S. Gebauer, G. J. Krauss, I. Thondorf, and W. Vogt, *Tetrahedron Lett.*, **36**, 6221 (1995).
95TL8075 D. St. C. Black, D. C. Craig, and N. Kumar, *Tetrahedron Lett.*, **36**, 8075 (1995).
96AJC311 D. St. C. Black, D. C. Craig, and N. Kumar, *Aust. J. Chem.*, **49**, 311 (1996).
96IC2413 R. Crescenzi, E. Solari, C. Floriani, A. Chiesi-Villa, and C. Rizzoli, *Inorg. Chem.*, **35**, 2413 (1996).
96JCS(P2)2359 E. Weber, J. Trepte, K. Gloe, M. Piel, M. Czugler, V. C. Kravtosov, Y. A. Simonov, J. Lipkowski, and E. V. Ganin, *J. Chem. Soc. Perkin Trans. 2*, 2359 (1996).
96T8925 D. S. C. Black, D. C. Craig, and D. B. McConnell, *Tetrahedron*, **52**, 8924 (1996).
96T15171 E. Alcalde, M. Alemany, and M. Gisbert, *Tetrahedron*, **52**, 15171 (1996).
96TL241 D. St. C. Black, D. C. Craig, N. Kumar, and D. B. McConnell, *Tetrahedron Lett.*, **37**, 241 (1996).
96TL4593 F. H. Kohnke, G. L. La Torre, and M. F. Parisi, *Tetrahedron Lett.*, **37**, 4593 (1996).

97CRV1713 A. Ikeda and S. Shinkai, *Chem. Rev.*, **97**, 1713 (1997).
97JCR(M)555 B. Konig, M. Rodell, I. Dix, and P. G. Jones, *J. Chem. Res.* (M), 555 (1997).
97JCS(CC)1461 J. Trepte, M. Czugler, K. Gloe, and E. Weber, *J. C. S. Chem. Commun.*, 1461 (1997).
97MI1 A. F. Pozharskii, A. T. Soldatenkov, and A. R. Katritzky, Heterocycles in Life and Society, Wiley, New York (1997).
97TL3607 S. Kumar, D. Paul, and H. Singh, *Tetrahedron Lett.*, **38**, 3607 (1997).
97TL7639 M. Mascal, J. L. Richardson, A. J. Blake, and W-Sheung Li, *Tetrahedron Lett.*, **38**, 7639 (1997).
98JA4319 A. Shivanyuk, C. Schmidt, V. Bohmer, E. F. Paulus, O. Lukin, and W. Vogt, *J. Am. Chem. Soc.*, **120**, 4319 (1998).
98JCS(CC)1 P. A. Gale, J. L. Sessler, and V. Kral, *J. C. S. Chem. Commun.*, 1 (1998).
98JCS(CC)9 V. Kral, P. A. Gale, P. Azenbacher Jr., K. Jursikova, V. Lynch, and J. L. Sessler, *J. C. S. Chem. Commun.*, 9 (1998).
98JCS(CC)181 S. Shinoda, M. Tadokoro, H. Tsukube, and R. Arakawa, *J. C. S. Chem. Commun.*, 181 (1998).
98MI1 C. D. Gutsche, Calixarenes Revisited, The Royal Society of Chemistry, Cambridge (1998).
98TA4289 W. Iwanek, *Tetrahedron Asymm.*, **9**, 4289 (1998).
98TL8833 C. Schmidt, I. Thondorf, E. Kolehmainen, V. Bohmer, W. Vogt, and K. Rissanen, *Tetrahedron Lett.*, **39**, 8833 (1998).
99ACR729 S. Ibach, V. Prautzsch, F. Vogtle, C. Chartroux, and K. Gloe, *Acc. Chem. Res.*, **32**, 729 (1999).
99CEJ356 G. Cafeo, M. Giannetto, F. H. Kohnke, G. L. La Torre, M. F. Parisi, S. Menzer, A. J. P. White, and D. H. Williams, *Chem. Eur. J.*, **5**, 356 (1999).
99H2807 K. Ito, Y. Ohba, T. Tamura, T. Ogata, H. Watanabe, Y. Suzuki, T. Hara, Y. Morisawa, and T. Sone, *Heterocycles*, **51**, 2807 (1999).
99JA6751 P. C. B. Page, H. Heaney, and E. P. Sampler, *J. Am. Chem. Soc.*, **121**, 6751 (1999).
99JCS(CC)295 E. Alcalde, C. Alvarez- Rua, S. Garcia-Granda, E. Garcia-Rodriguez, N. Mesquida, and L. Perez-Garcia, *J. C. S. Chem. Commun.*, 295 (1999).
99JOC7717 S. Kumar, G. Hundal, D. Paul, M. S. Hundal, and H. Singh, *J. Org. Chem.*, **64**, 7717 (1999).
99OL1035 E. Alcalde, S. Ramos, and L. Perez-Garcia, *Org. Lett.*, **1**, 1035 (1999).
99OM606 R. Crescenzi, E. Solari, C. Floriani, N. Re, A. Chiesi-Villa, and C. Rizzoli, *Organometallics*, **18**, 606 (1999).
99T4803 D. St. C. Black, D. C. Craig, N. Kumar, and R. Rezaie, *Tetrahedron*, **55**, 4803 (1999).
99TL5927 V. Bohmer, S. Caccamese, G. Principato, and C. Schmidt, *Tetrahedron Lett.*, **40**, 5927 (1999).
2000AGE1496 G. Cafeo, F. H. Kohnke, G. L. La Torre, A. J. P. White, and D. J. Williams, *Angew. Chem., Int. Ed.*, **39**, 1496 (2000).
2000EJO3937 C. Schmidt, T. Straub, D. Falabu, E. F. Paulus, E. Wegelius, E. Kolehmainen, V. Bohmer, K. Rissenen, and W. Vogt, *Eur. J. Org. Chem.*, 3937 (2000).
2000JA12061 J. L. Sessler, P. Anzenbacher, J. A. Shriver, K. Jursikova, V. M. Lynch, and M. Marques, *J. Am. Chem. Soc.*, **122**, 12061 (2000).
2000JCS(P1)1037 S. Kumar, D. Paul, G. Hundal, M. S. Hundal, and H. Singh, *J. Chem. Soc. Perkin Trans. P1*, 1037 (2000).

2000JCS(P1)2295 S. Kumar, G. Hundal, D. Paul, and M. S. Hundal, *H. Singh. J. Chem. Soc. Perkin Trans. 1*, 2295 (2000).

2000MI1 J. N. Sessler and P. A. Gale, in *"Porphyrin Handbook"* (K. M. Kadish, K. M. Smith and R. Guilard, eds.), p. 45, Academic Press, New York (2000).

2000MI2 S. Kumar, D. Paul, and H. Singh, *J. Inclusion Phenomena Macrocyclic Chem.*, **37**, 371 (2000).

2000OL3115 A. Nagarajan, Y-Sung Jang, and C-Hee Lee, *Org. Lett.*, **2**, 3115 (2000).

2000T8513 D. S. C. Black, N. Kumar, and D. B. McConnell, *Tetrahedron*, **56**, 8513 (2000).

2000TL2919 Y-Sung Jang, H-Je Kim, P-Ho Lee, and C-Hee Lee, *Tetrahedron Lett.*, **41**, 2919 (2000).

2001CCR57 P. A. Gale, P. Anzenbacher Jr., and J. L. Sessler, *Coord. Chem. Rev.*, **222**, 57 (2001).

2001CEJ465 T. Gerkensmeier, J. Mattay, and C. Nather, *Chem., Eur. J.*, **7**, 465 (2001).

2001JCS(P1)1304 J. Guillard, C. Lamazzi, O. Meth-Cohn, C. W. Rees, A. J. P. White, and D. J. Williams, *J. Chem. Soc. Perkin Trans. 1*, 1304 (2001).

2001JCS(P1)3297 V. Beneteau, O. Meth-Cohn, and C. W. Rees, *J. Chem. Soc. Perkin Trans. 1*, 3297 (2001).

2001JHC293 K. Ito, Y. Ohba, T. Tamura, T. Ogata, H. Watanabe, Y. Suzuki, T. Hara, Y. Morisawa, and T. Sone, *J. Heterocycl. Chem.*, **38**, 293 (2001).

2001JOC2281 E. Alcalde, C. Ayala, I. Dinares, N. Mesquida, and F. Sanchez-Ferrando, *J. Org. Chem.*, **66**, 2281 (2001).

2001OM1276 J. C. Garrison, R. S. Simons, J. M. Talley, C. Wesdemiotis, C. A. Tessier, and W. J. Youngs, *Organometallics*, **20**, 1276 (2001).

2001T2103 S. Taniguchi, H. Hasegawa, S. Yanagiya, Y. Tabeta, Y. Nakano, and M. Takahashi, *Tetrahedron*, **57**, 2103 (2001).

2001T2203 D. St. C. Black, N. Kumar, and D. B. McConnell, *Tetrahedron*, **57**, 2203 (2001).

2001T7323 A. Nagarajan, J-Won. Ka, and C-Hee Lee, *Tetrahedron*, **57**, 7323 (2001).

2002CEJ474 E. Alcalde, N. Mesquida, L. Perez-Garcia, S. Ramos, M. Alemany, and M. L. Rodriguez, *Chem. Eur. J.*, **8**, 474 (2002).

2002CEJ1134 J. L. Sessler, W. Seob Cho, V. Lynch, and V. Kral, *Chem. Eur. J.*, **8**, 1134 (2002).

2002CEJ3148 G. Cafeo, F. H. Kohnke, G. L. La Torre, M. F. Parisi, R. P. Nascone, A. J. P. White, and D. J. Williams, *Chem. Eur. J.*, **8**, 3148 (2002).

2002JCS(CC)232 J. Guillard, O. Meth-Cohn, C. W. Rees, A. J. P. White, and D. J. Williams, *J. C. S. Chem. Commun.*, 232 (2002).

2002JCS(CC)810 D. S. C. Black, D. C. Craig, and R. Rezaie, *J. C. S. Chem. Commun.*, 810 (2002).

2002JCS(CC)1686 R. Tanaka, T. Yano, T. Nishioka, K. Nakajo, B. K. Breedlove, K. Kimura, I. Kinoshita, and K. Isobe, *J. C. S. Chem. Commun.*, 1686 (2002).

2002JOC8463 S. Ramos, E. Alcalde, G. Doddi, P. Mencarelli, and L. Perez-Garcia, *J. Org. Chem.*, **67**, 8463 (2002).

2002OL2695 G. Cafeo, F. H. Kohnke, M. F. Parisi, R. P. Nascone, G. L. La Torre, and D. J. Williams, *Org. Lett.*, **4**, 2695 (2002).

2002T5125 D. S. C. Black, D. C. Craig, N. Kumar, and R. Rezaie, *Tetrahedron*, **58**, 5125 (2002).

2002TL7945 Y. Miyazaki, T. Kanbara, and T. Yamamoto, *Tetrahedron Lett.*, **43**, 7945 (2002).
2002TL9493 E. C. Lee, Y-Kwang Park, J-Ho Kim, H. Hwang, Y-Rok Kim, and C-Hee Lee, *Tetrahedron Lett.*, **43**, 9493 (2002).
2003JA13646 J. L. Sessler, D. An, W-Seob Cho, and V. Lynch, *J. Am. Chem. Soc.*, **125**, 13646 (2003).
2003TL1359 X. Yang and C. R. Lowe, *Tetrahedron Lett.*, **44**, 1359 (2003).
2004JA9669 M. C. Letzel, B. Decker, A. B. Rozhenko, W. W. Schoeller, and J. Mattay, *J. Am. Chem. Soc.*, **126**, 9669 (2004).
2004S865 R. Pajewski, R. Ostaszewski, K. Ziach, A. Kulesza, and J. Jurczak, *Synthesis*, 865 (2004).
2004T1895 G. Cafeo, D. Garozzo, F. H. Kohnke, S. Pappalardo, M. F. Parisi, R. P. Nascone, and D. J. Williams, *Tetrahedron*, **60**, 1895 (2004).
2004TL299 M-Y. Song, H-K. Na, E-Y. Kim, S-J. Lee, K. I. Kim, E-M. Baek, H-S. Kim, D. K. An, and C-H. Lee, *Tetrahedron Lett.*, **45**, 299 (2004).

Organometallic Complexes of B-, Si- (Ge-), and P- (As-, Sb-) Analogues of Pyridine

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Abbreviations

acac	acetylacetonate
AN	acetonitrile
bpy	2,2′-bipyridine
Bu	butyl
cod	cyclooctadiene-1,4
COE	cyclooctene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
DMF	dimethylformamide
Et	ethyl
LUMO	lowest unoccupied molecular orbital
Me	methyl
Nu	nucleophile
Ph	phenyl
Pr	propyl
py	pyridine
solv	solvent
THF	tetrahydrofuran
THP	tetrahydropyran
TMEDA	tetramethylenediamine

ADVANCES IN HETEROCYCLIC CHEMISTRY
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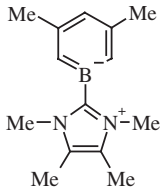
I. Boratabenzenes

A. Introduction

Boratabenzene does not exist due to the low-lying LUMO of the σ(B)-type (89OM733). It is stabilized in neutral or anionic adducts (97OM1501). Boratabenzene, C_5H_5B, is not isoelectronic with benzene but is planar (84ZN(A)678, 87ZN(A)352, 90JA1707) and forms stable adducts. It is aromatic and its reactivity is due to the σ-orbitals (97IJQC441). Quantum-chemical calculations of [M(η^6-$C_5H_5BH)_2$] (M = Cr, Mn, Fe, Co) revealed that boratabenzene is intermediate in ligand characteristics between benzene and cyclopentadienyl, and it is closer in properties to cyclopentadienyl, although it has a better tendency to accept electrons (81JOM(208)183). Boratabenzene (88AGE295) is unstable but acquires stability in the boron-centred adducts (85CB1644) and predominantly $\eta^6(\pi)$-complexes (86ADOC199). Theoretical estimates point to planarity although with distortion and π-electron delocalization in this heteroring (82JA3785, 84ZN(A)678, 87ZN(A)352, 90JA1707). The η^6-coordination mode of boratabenzenes is nevertheless characterized by a stronger metal–carbon than metal–boron bonding (90CB505). Substitution of one of the CH moieties in the benzene ring with an isoelectronic BH^- framework leading to boratabenzenes is accompanied by an increase in the π-electron density in the heteroring (90JA1707, 96AGE292). The η^6-donor function is regarded as a common coordination mode for boratabenzenes (96JA2291, 97JA7155, 97JA9305, 98JA1082, 98OM3883, 03OM910) and boratanaphthalenes (85CB1644, 85ZN(B)1327, 86ZN(B)167, 02OM1949). However, deviations from the η^6-function become possible for the early transition metal complexes when the donor substituent is present at the boron atom.

B. Complexes of Non-Transition Elements

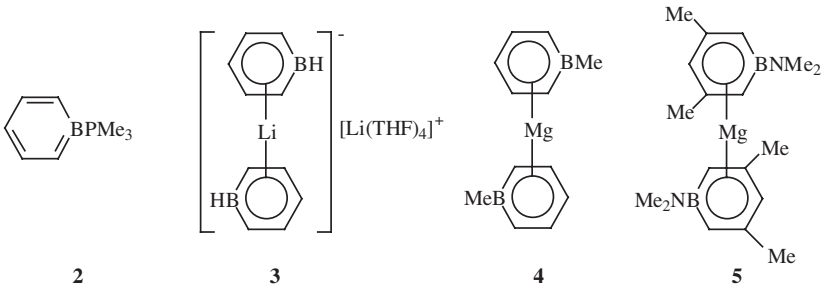
Of interest is the imidazol-2-ylidene adduct of structure **1** from the lithium salt of dimethylamino-3,4-dimethylboratabenzene and 1,3,4,5-tetramethylimidazol-2-ylidene (00OM3751). The B–C bond between the two heterocycles is purely single, and conjugation between the two heterorings is absent.



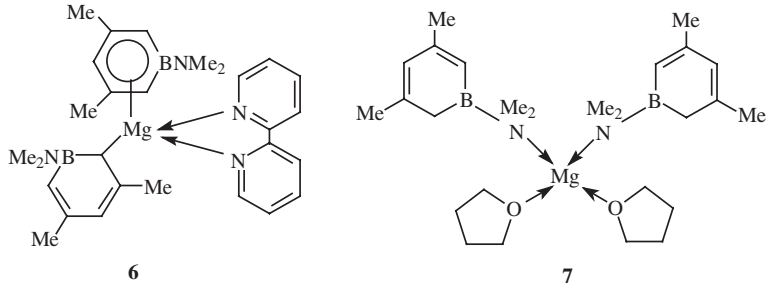
1

Boratabenzenes as anionic ligands (78JOM(160)17, 01ADOC101, 01JCS(CC)619, 01OM468) are rarely used in the complexes of non-transition metals. Interaction of the trimethylphosphine adduct of boratabenzene **2** with lithium aluminium hydride in THF gives the lithium sandwich of a BH-boratabenzene **3** (95JA8480), the second

representative in this group after $[Fe(C_5H_5BH)_2]$ (79JA7066). Another lithium sandwich is $[Li(Me_2NC_2H_4NMe_2)(\eta^6\text{-}C_5H_5B(NMe_2)]$ (93OM2891, 98OM1254). Non-transition metal species of boratabenzene also involve those of sodium (00JA3969) and potassium (97JA7155, 03EJIC2175). Bent sandwiches are formed from germanium(II), tin(II), and lead(II) chlorides in the compounds $[M(\eta^6\text{-}C_5H_5BMe)_2]$ (97MI1). Magnesocene follows from 2-$Me_3SnC_5H_5BMe$ and dimethyl magnesium and is formulated as $[(\eta^6\text{-}C_5H_5BMe)_2Mg]$, tetramethyltin being the other product (97MI1). Dimethyl magnesium with 2-$(Me_3Sn)C_5H_4BMe$ and 2-$Me_3Sn(3,5\text{-}Me_2C_5H_3BNMe_2)$ forms sandwiches **4** and **5** (00IC5579). Sandwich **5** forms adduct **6** with 2,2′-bipyridine. Adduct-formation is accompanied by a switch in the coordination mode of one of the boratabenzene moieties from η^6 to η^1(C). The adduct of **5** with THF has an unprecedented coordination pattern, **7**.

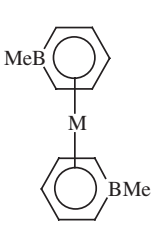


2 **3** **4** **5**



6 **7**

In compounds 2-$(Me_3E)C_5H_5BMe$ (E = Si, Ge, Sn, Pb) boratabenzenes reveal the η^1(B) function (97OM926). 1,2-Dihydroborinine 2-$(Me_2Sn)C_5H_5BMe$ with $PbCl_2$, $SnCl_2$, and GeI_2 form the η^6-sandwiches **8** (M = Pb, Sn, Ge) (99OM4747). The lead complex can alternatively be prepared from LiC_5H_5BMe (95OM471) and $PbCl_2$. Complex **8** (M = Pb) with TMEDA forms an adduct $[Pb(C_5H_5BMe)_2(TMEDA)]$ and with 2,2′-bipyridine-$[Pb(C_5H_5BMe)_2(bpy)]$, where the incoming ligands form chelates at the lead atom. Thallium derivatives $[Tl(C_5H_5BR)]$ (R = Me, Ph) have a bridging $\mu\text{-}\eta^6\text{:}\eta^6$ mode (78JOM(153)265), while η^1(B)-coordination is observed in $[InMe(C_5H_5BMe)_2]$ (97ZAAC1098). Lithium 1-(dimethylamino)-3,4-dimethylamino-boratabenzene with $PbCl_2$ gives **9** (01EJIC3013). The low stability of **9** is due to the influence of the 1-NMe_2-substituent. $Li[3,5\text{-}Me_2C_5H_3BN(SiMe_3)_2]$ and GeI_2, $SnCl_2$ or $PbCl_2$ form species **10** (E = Ge, Sn, Pb) possessing thermal stability.



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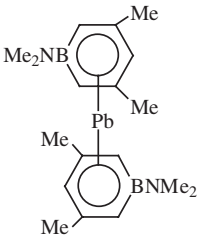

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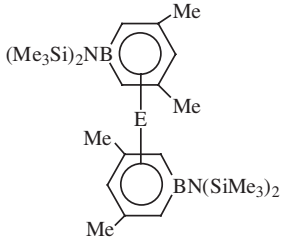
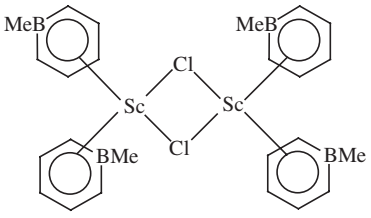


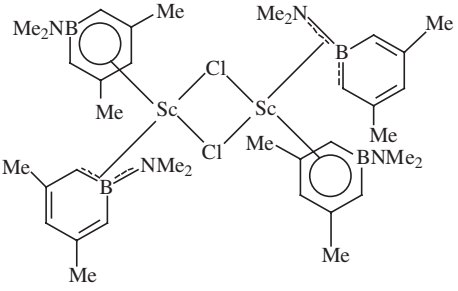
10

C. Complexes of the Scandium and Titanium Group Metals

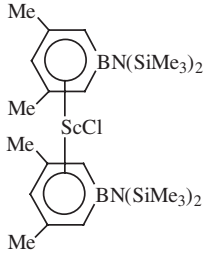
Lithium salts of 1-methylboratabenzene, 1-dimethylamino-3,5-dimethylboratabenzene and 1-bis(trimethylsilyl)amino-3,5-dimethylboratabenzene react with $ScCl_3$ in toluene at elevated temperature to yield complexes **11**, **12** and **13** having different structures and compositions (03OM5496). The structure **11** is characterized by two sandwich units doubly bridged by the chloride moieties. Compound **12** seems similar to **11** but one boratabenzene ligand is coordinated in an unusual η^3(NBC) mode, while the second one is η^6-coordinated. Compound **13** is mononuclear.



11



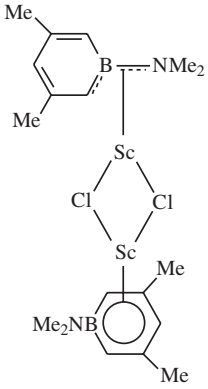
12



13

Derivatives $[M_2(\mu\text{-}Cl)_2(\eta^6\text{-}C_5H_5BMe)_4]$ (M = Sc, Gd, Ti) follow from the lithium salt of 1-methylborinine and MCl_3 (M = Sc, Gd, Ti) (97MI1). The same type of reaction is noted for $ZrCl_4$ and $HfCl_4$ to yield $[MCl_2(\eta^6\text{-}C_5HBMe)_2]$ (M = Zr, Hf). 2-$Me_3SnC_5H_5BMe$ interacts with $[(\eta^5\text{-Cp})TiCl_3]$ to yield $[(\eta^{-5}\text{-Cp})TiCl_2(\eta^6\text{-}C_5H_5BMe)]$ and with titanium(IV) chloride to give $[(\eta^6\text{-}C_5H_5BMe)TiCl_3]$. The

adduct [Li($C_5H_5BPMe_3$)] with [$Ph_3Sc(THF)_3$] gives the $\eta^6(\pi)$-complex of composition [($C_5H_5BPMe_3$)$ScPh_3$] (99JA8112). Another example is [(η^6-C_5H_5BMe)Sc(μ-Cl)]$_2$ (99OM5496). Lithium 1-methylboratabenzene with yttrium(III) chloride gives [(η^6-C_5H_5BMe)Y(μ-Cl)]$_2$ (01IC3117). [Li(3,5-$Me_2C_5H_3BNMe_2$)] with scandium(III) chloride gives **14** (02EJIC31), where one of the heteroaromatic ligands is η^3(N–B–C) coordinated and the other is classically η^6-coordinated. The same starting ligand with YCl_3 and $LuCl_3$ gives fully η^6-coordinated sandwiches but with unique lithium chloride bridges, **15** (M = Y, Lu). **15** (M = Y) with sodium acetylacetonate gives species **16**. With $SmCl_3$ in THF, [(η^6-3,5-$Me_2C_5H_3BNMe_2$)Sm(μ-Cl)$_2$Li(THF)] is the product. Similar complex **17** follows from YCl_3 in THF. When the bulky group is introduced at the nitrogen atom, [Li{3,5-$Me_2C_5H_3BN(SiMe_3)_2$}], interaction with MCl_3 (M = Sc, Y, Lu) leads to the mononuclear complexes **18** (M = Sc, Y, Lu). The same type of complex follows from [Li(3,5-$Me_2C_5H_3BNPr^i_2$)] and $ScCl_3$. With YCl_3 and $SmCl_3$ in THF, differing species of composition [(η^6-3,5-$Me_2C_5H_3BNPr^i_2$)M(μ-Cl)$_2$Li(THF)$_2$] follow. The reaction of the lithium bis(boratabenzene) salt with $LuCl_3$ in THF and THP gives the B,B-bridged *ansa*-complexes [(3,5-$Me_2C_5H_3BNMeCH_2$)$_2$Lu(μ-Cl)$_2$LiL$_2$] (L = THF, THP).



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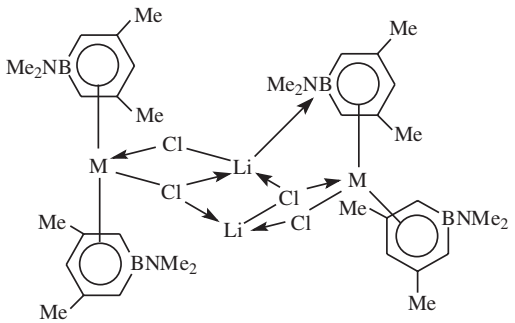

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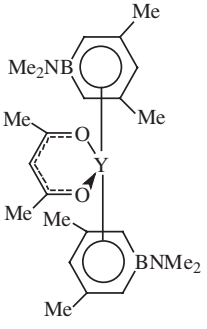

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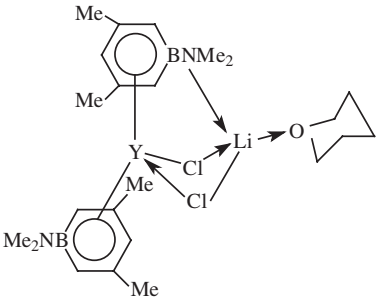

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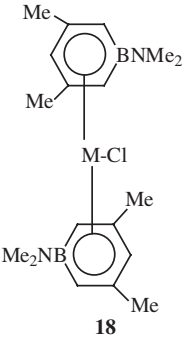
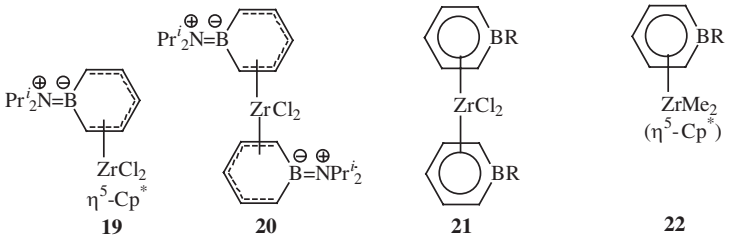
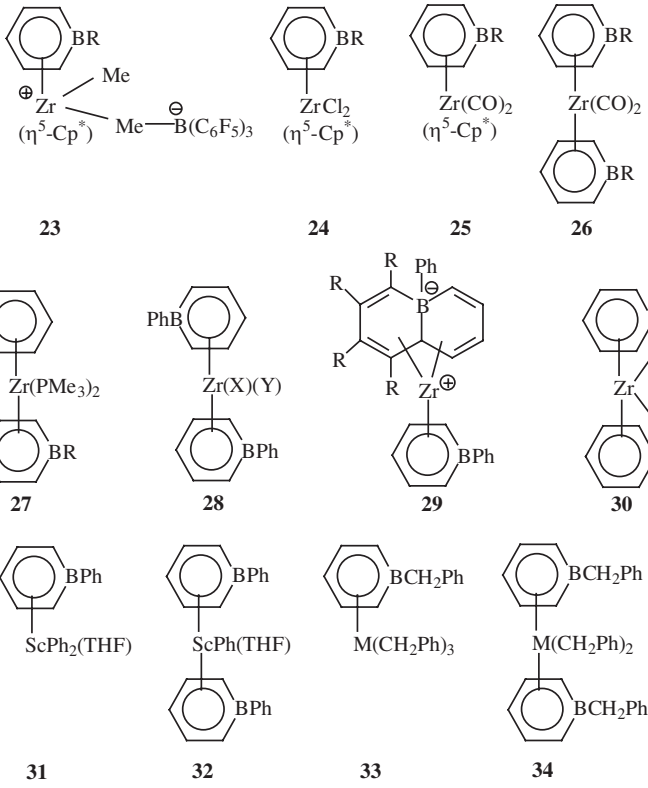


18

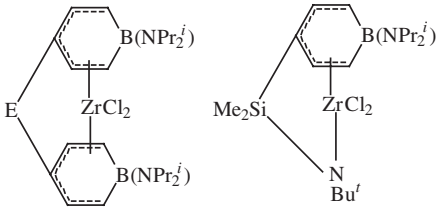
Boratabenzene lithium with [(η^5-Cp*)$ZrCl_3$] gives the η^5-coordinated species **19** and with zirconium chloride – the full sandwich **20** (96JA2291, 97OM2492). The latter

reacts with methyl lithium to yield $[(C_5H_5BNPr^i_2)_2ZrMe_2]$. Photolysis of the dimethyl derivative in CD_2Cl_2 gives the monomethyl chloride that eventually transforms back to **21** (99JA1288). Species **19** and **20** are catalysts in ethylene polymerization. The catalytic potential of the boratabenzene complexes may be controlled by the nature of the substituent at the boron heteroatom (96JA10317, 99JA1513, 03CRV283). Species like **20** [R = NPr^i_2 (96JA2291), OEt (97JA9305), Me (97OM3751), and Ph (97OM2492) are catalysts for olefin polymerization, provided they are activated with methylaluminoxane. The catalytic activity is related to the violation of aromaticity within the boratabenzene ring, weak zirconium – boron interactions enhancing reactivity of the zirconium site, and strong boron – nitrogen interaction in case of the NPr^i_2-substituent (93OM2891, 96OM387). As a result, $C_5H_5B(NPr^i_2)$ coordinates in an η^5-fashion. Difficulties in the preparation of the $ZrMe_2$ analogues of **21** (97JOM(535)29) lead to another way of preparation where the $ZrCl_2$ moiety is methylated prior to the boratabenzene complexation (98JA6037). Reaction of [(η^5-Cp*)ZrMeCl] with lithium or sodium salts of C_5H_5BR (R = NMe_2, OEt, Ph) gives **22** (R = NMe_2, OEt, Ph) (00JA1371). Treatment of **22** (R = NMe_2, OEt, Ph) with $B(C_6F_5)_3$ gives the zwitterionic products **23** (R = NMe_2, OEt, Ph) active in olefin polymerization (99JA1288). Complexes **24** (R = NMe_2, OEt, Me, Ph) in the presence of magnesium give **25** (R = NMe_2, OEt, Me, Ph) (00JA1371). The same reaction is observed for **18** (R = NMe_2, OEt, Me, Ph) and the product is **26** (R = NMe_2, OEt, Me, Ph). Trimethyl aluminium forms an adduct with $[(C_5H_5BOEt)(\eta^5\text{-Cp*})ZrCl_2]$ via the oxygen atom of the ethoxymoiety (99JA1288). Sodium alkoxyboratabenzene ligands with $ZrCl_4(THF)_2$ give species **21** (R = Me, *t*-Bu) (02OM3189). Zirconium(IV) species react with *n*-butyl lithium in the presence of trimethylphosphine to yield **27** [R = N(*i*-Pr)$_2$, Ph], where the heteroring is definitely η^6-coordinated (97AGE2014). Detailed structural analysis showed that the coordination mode in **21** is in fact η^5 without the boron atom (96OM387), while in **27** it is η^6. Complex **27** (R = Ph) enters an oxidative addition with methyl iodide to yield **27** (X = I, Y = Me) and diphenyl disulphide to produce **28** (X = Y = SPh). With ethyne and 2-butyne, adducts **29** (R = H, Me) are obtained (99OM4234). With 1,3-diynes RC≡CC≡CR, R = Me, Et, Ph), **27** (R = NPr^i_2, Ph), the products are **30** (X = NPr^i_2, Ph; R = Me, Et, Ph), where at X = NPr^i_2, the η^5-coordination is observed, a feature of the zirconium(IV) complex (99JOM(581)92). Adduct $C_5H_5B\text{-}PMe_3$ with $[Ph_3Sc(THF)_2]$ gives **31**, and further with trimethylphosphine **32** (99JA8112). The same starting adduct reacts with tetrabenzyl zirconium and hafnium to give **33** (M = Zr, Hf), and for the zirconium derivative further reaction with $C_5H_5B\text{-}PMe_3$ affords **34**.



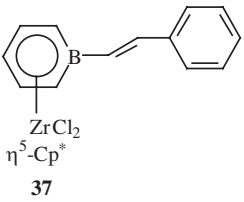


Bridged species **35** (E = CH_2CH_2, $SiMe_2$) are possible catalysts for polymerization of alkenes (98OM3883, 99JOM(581)92). Complexes **36** (M = Ti, Zr) are prepared by consecutive treatment of the lithium salt of 1-di-*iso*-propylaminoboratabenzene by dimethyldichlorosilane, *tert*-butylamine, *tert*-butyl lithium, and finally titanium(IV) or zirconium(IV) chloride (99OM1363). This is a typical situation for the complexes of the early transition metals where there is a reduction in the coordination mode $\eta^6 \rightarrow \eta^5$, pulling the boron heteroatom out of bonding to the metal centre. The products catalyse ethylene polymerization. Complex **36** catalyses ethylene polymerization, while the analogue with the ethoxysubstituent at the boron atom is active in oligomerization leading to small 1-alkenes (97JA9305).



Sodium salts of boratastilbene, 4-boratastyrylstilbene and 1,4-bis(boratastyryl)benzene with [(η^5-Cp*)$ZrCl_3$] form the η^6-complexes **37**, **38** and **39**, respectively

(02JOM(642)275). Sodium boratastilbene with $[ZrCl_4(THF)_2]$ forms sandwich **40**. Species **37** and **38** are efficient catalysts for ethylene polymerization. Interaction of the appropriate boratabenzene ligand with lithium di-*iso*-propylamide and then zirconium(IV) chloride gives **41** (03OM203). Similarly, **42** can be obtained.



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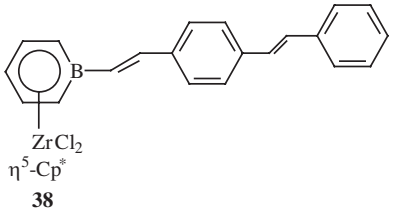

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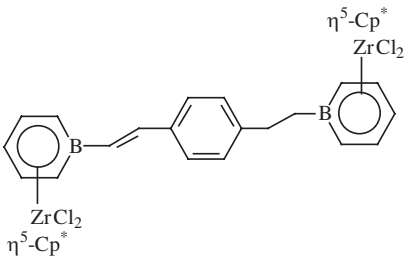

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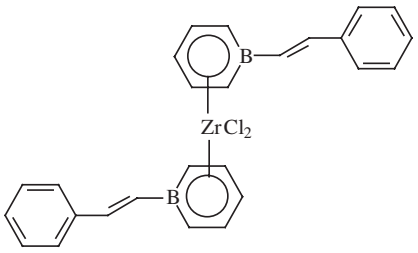

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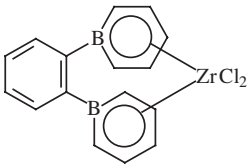

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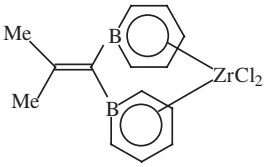
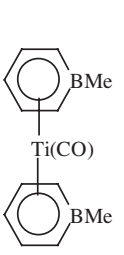


42

The lithium salt of 1-methylboratabenzene reacts with $[TiCl_3(THF)_3]$ followed by magnesium powder in an atmosphere of carbon monoxide gives **43** (03AGE4510). The product reacts with acetylene in toluene to give a mixture of the products **44**–**46**. Structural data for **45** point to the η^8-borataoctacyclotetraene ligand. Similar reaction occurs between **43** and trimethylsilylacetylene to yield **47**.



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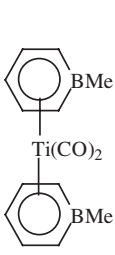

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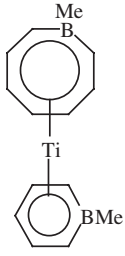

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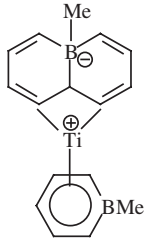

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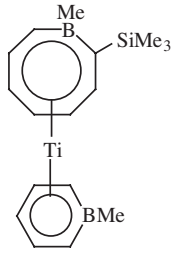
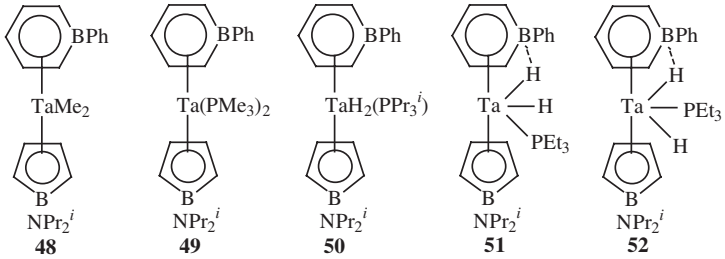


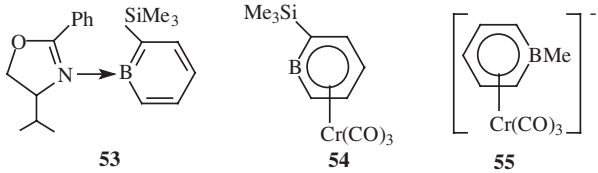
47

D. Complexes of the Vanadium and Chromium Group Metals

The reactivity pattern of the boratabenzene $\eta^6(\pi)$-complexes depends on the environment of the metal site and the nature of the exocyclic substituents at the boron atom (97OM2492). The mixed–ligand complex **48** (98JA7791) reacts with hydrogen in the presence of PMe_3 to give the only product **49** (99JA1513). However, if the phosphine contains bulkier groups, PPr^i_3, the dihydride product **50** follows. Triethylphosphine in a similar fashion gives a mixture of *cis*-, **51**, and *trans*-, **52**, isomers with a Ta–H···B three-centre interaction (94OM619, 98JA7791).

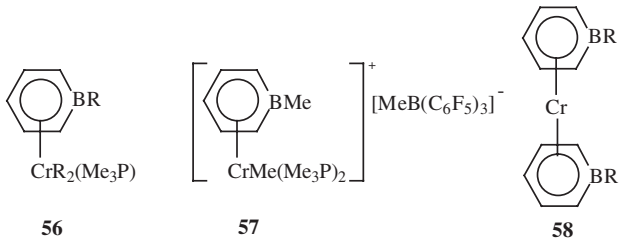


The boratabenzene adduct **53** with $[Cr(CO)_3(AN)_3]$ produces the $\eta^6(\pi)$-species **54** along with a free 2-phenyloxazoline (97AGE267, 97JOC8286, 99CSR51). The reaction of sodium 1-methylboratabenzene with $[Cr(CO)_3(NH_3)_3]$ is a simple route to the anionic complexes **55**, where Na, PPh_4, Hg, H may serve as cations (83JOM(254)143).

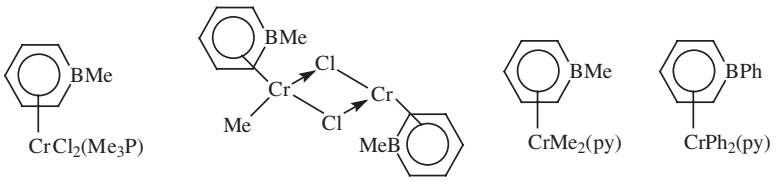


The lithium salt of 1-phenylboratabenzene with chromium(II) chloride gives the chromium(II) sandwich $[(\eta^6\text{-}C_5H_5BPh)_2Cr]$ lacking catalytic activity (77CB816). The adduct $C_5H_5BPMe_3$ reacts with $[Ph_3Cr(THF)_3]$ to yield the chromium(III) $\eta^6(\pi)$-complex **56** (R = Ph) (00JA730). $[CrCl_3(THF)_3]$ with MeMgBr gives $[CrMe_3]$ *in situ*, which on reacting with trimethylphosphine forms adduct **56** (R = Me). Both **56** (R = Me, Ph) reveal catalytic activity in ethylene polymerization. Species **56** (R = Me) with $B(C_6F_5)_3$ in the presence of trimethylphosphine gives **57**. The trimethylphosphine adduct of boratabenzene with $[CrPh_3(THF)_3]$ gives the chromium(III) species **56** (R = Ph), and with $[CrCl_3(THF)_3]$ in the presence of methylmagnesium bromide **56** (R = Me). Sandwiches **58** (R = Me, Ph) follow from the corresponding potassium salt and $CrCl_2 \cdot THF$ (77CB1167, 78JOM(157)327). Lithium salts of 1-methyl-, 1-dimethylamino-, and 1-phenylboratabenzene with $[CrCl_3(THF)_3]$ give full sandwiches **58** (R = Me, NMe_2, Ph), where the Cr(II) oxidation state is stabilized (00OM3948). The trimethylphosphine adduct of

boratabenzene with $[MeCrCl_2(THF)_3]$ gives, however, the chromium(III) species **59**. The pyridine adduct gives the dinuclear species **60** in low yield. If $[CrCl_3(THF)_3]$ is first treated with methylmagnesium bromide and then pyridine adduct, the Cr(III) species **61** follows. The pyridine adduct interacts directly with $[CrPh_3(THF)_3]$ to give **62** (00JCS(CC)1209, 00OM3948). The chromium(III) monomer appears to catalyse ethylene polymerization.



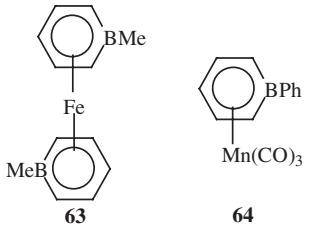
56 **57** **58**



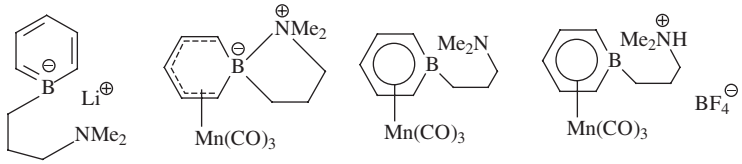
59 **60** **61** **62**

E. Complexes of the Manganese and Iron Groups

The η^6-coordination mode of 1-substituted boratabenzenes is well documented (70AGE805, 82MI1, 86ADOC199, 95MI1, 97PSS295, 98JA3883, 99OM3406), e.g. in the complexes **63** (75JA6865) and **64** (73AGE764). Boratabenzene **65** reacts with $[Mn(CO)_3(AN)_3](PF_6)$ to yield the η^5-coordinated species **66** (97OM163) in marked contrast to the η^6-1-phenylboratabenzene complex containing the same tricarbonylmanganese moiety (74CB3786). The product **66** is in equilibrium with the opened isomer **67** in solution (97OM163). With tetrafluoroboric acid, a mixture of isomers **66** and **67** gives the ammonium salt **68**.

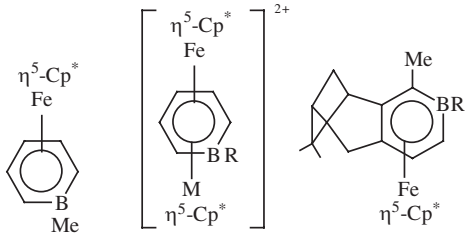


63 **64**

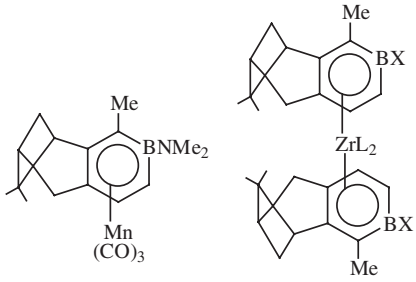


65 **66** **67** **68**

Boratabenzene anions of composition $[C_5H_5BR]^-$ give rise to a variety of sandwich complexes, among them are $[(\eta^6\text{-}C_5H_5BMe)V(CO)_4]$ (84JOM(265)225), $[(\eta^6\text{-}C_5H_5BPh)Mn(CO)_3]$ (74CB3786), $[Fe(\eta^6\text{-}C_5H_5BBu\text{-}t)_2]$ (71JA1804, 75JA6865, 93JOM(450)171), $[(\eta^6\text{-}C_5H_5BMe)Fe(CO)(\mu\text{-}CO)]_2$ (74CB3786). Boratabenzene predominantly forms sandwiches with transition-metal derivatives (95MI1, 95OM834, 96JA2291, 96OM387). However, triple-decker formation appears to be a new trend (93JOM(459)1), inclusive of the product of interaction of $[(\eta^5\text{-Cp*})Ru(\eta^6\text{-}C_5H_5BMe)]$ and $[(\eta^5\text{-Cp*})Ru(OCMe_2)_3]^+$ and formulated as $[(\mu\text{-}\eta^6\text{-}C_5H_5BMe)Ru(\eta^5\text{-Cp*})_2]$ or the product of interaction of the same boratabenzene sandwich with $[(\eta^5\text{-Cp*})Rh(OCMe_2)_3]^{2+}$ to give the triple-decker cationic species of composition $[(\mu\text{-}\eta^6\text{-}C_5H_5BMe)Ru(\eta^5\text{-Cp*})Rh(\eta^5\text{-Cp*})]^{2+}$. The lithium salt of $C_5H_5BMe^-$ (95OM471) with $[(\eta^5\text{-Cp*})Fe(acac)]_x$ gives **69** (96OM5236) along with $[Fe(\eta^5\text{-Cp*})_2]$ and $[Fe(\eta^6\text{-}C_5H_5BMe)_2]$. The same product is formed neatly from $[Li(C_5H_5BMe)]$ and $[(\eta^5\text{-Cp*})Fe(AN)_3](PF_6)$. Further reaction of **69** with $[(\eta^5\text{-Cp*})Fe(AN)_3]$ or $[(\eta^5\text{-Cp*})Ru(AN)_3](CF_3SO_3)$ gives the stacked cationic products **70** (M = Fe, Ru; $n = 1$). Complex **69** with $[(\eta^5\text{-Cp*})M(MeNO_2)_x]^{2+}$ (M = Rh, Ir) gives **70** (M = Rh, Ir; $n = 2$). Interaction of $[(\eta^4\text{-cod})Rh(\eta^6\text{-}C_5H_5BMe)]$ (76CB2382) with $[(\eta^4\text{-cod})Rh(solv)_x]^+$ gives the triple-deckers $[(\mu\text{-}\eta^6\text{-}C_5H_5BMe)\{Rh(\eta^4\text{-cod})\}_2]^+$ (solv = CH_2Cl_2, $MeNO_2$) (96OM5236). The scope of the triple-deckers was broadened to $[(\eta^5\text{-Cp*})Fe(\mu\text{-}\eta^6\text{-}C_5H_5BMe)ML_n]^{2+}$ (M = Co, $L_n = \eta^5$-Cp*; M = Rh, Ir, $L_n = \eta^5$-Cp; M = Ru, $L_n = C_6H_6$, 1,3,5-$C_6H_3Me_3$, C_6Me_6) (02JOM(649)136). The lithium salt of a pinene-fused boratabenzene dimethylamino derivative also reacts with $[(\eta^5\text{-Cp*})Fe(AN)_3](PF_6)$ to yield **71** (R = NMe_2) (00EJIC979). Interaction with copper(I) iodide has also been studied (99OM3406). In methanol medium, **70** (R = NMe_2) is converted into **71** (R = OMe). The latter with methyl lithium gives **71** (R = Me). The same starting ligand with $[Mn(CO)_3Br(py)_2]$ gives **72**. With zirconium(IV) chloride, **73** (L = Cl, X = NMe_2) is obtained. Complexes **73** (L = Cl, OMe; L = Cl, X = Me; L = Me, X = NMe_2) were also prepared.

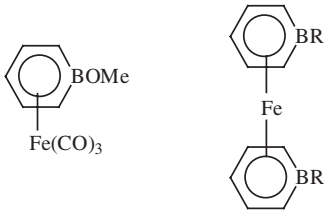


69 **70** **71**



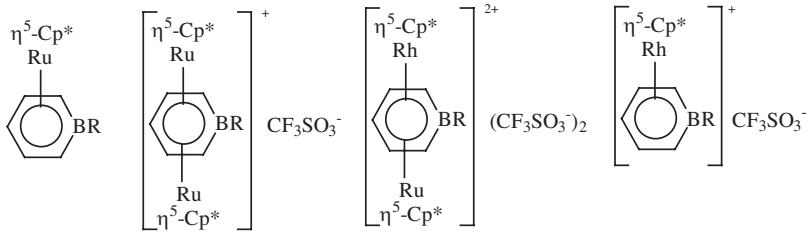
72 **73**

1-Methoxyboratabenzene complex **74** formed from the corresponding ligand and $[Fe_2(CO)_9]$ on thermolysis gives the full sandwich **75** (R = MeO). Reduction of **75** using lithium aluminium hydride gives sandwich **75** (R = H), which on treatment with *n*-butyl lithium gives **75** (R = *n*-Bu) (81JOM(207)345).



74 **75**

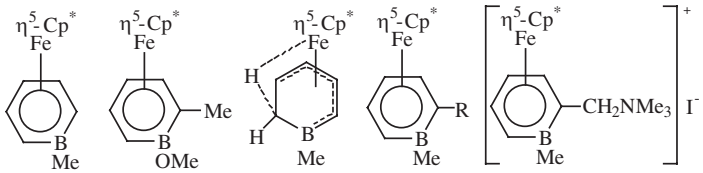
Interaction of $[Li(TMEDA)](C_5H_5BNMe_2)$ with $[(\eta^5\text{-Cp*})RuCl]_4$ gives sandwich **76** (R = NMe_2) (93JOM(459)1). With methanol, the product gives **76** (R = OMe), and then with methyl lithium **76** (R = Me) is formed. The latter sandwich on reaction with $[(\eta^5\text{-Cp*})RuCl]_4$ and silver triflate yields the cationic triple-decker complex **77**, and with $[(\eta^5\text{-Cp*})Rh(OCMe_2)_3](CF_3SO_3)$ the labile dicationic triple-decker complex **78**. The boratabenzene transfer with formation of **79** occurs when **78** reacts with naphthalene. Similar complex, $[(\eta^5\text{-Cp*})Rh(\eta^6\text{-}C_5H_5BPh)]^+$ is known (69CB607).



76 **77** **78** **79**

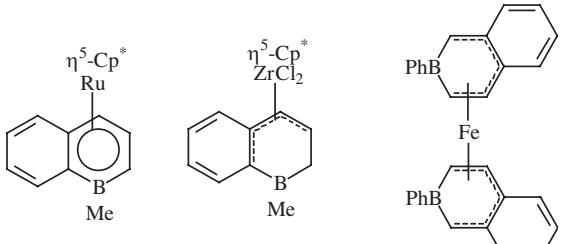
Reaction of $[Li(C_5H_5BMe)]$ with $[(\eta^5\text{-Cp*})Fe(AN)_3](PF_6)$ gives complex **80** (97MI1). It can be chemically oxidized with $(NH_4)_2Ce(NO_3)_6$ to yield $[(\eta^5\text{-Cp*})Fe(\eta^5\text{-}C_5H_4Me)]$ and $B(OMe)_3$. With mercury(II) acetate, complex **81** is unexpectedly

formed. With triflic acid, **80** gives the protonation product **82**. Starting complex **80** undergoes H/D exchange, Vilsmeyer formylation with $POCl_3$/DMF to produce **83** (R = CHO), aminomethylayion with $CH_2(NMe_2)/CF_3COOH$/MeI to give **84**, and Friedel–Crafts acetylation to afford **83** (R = COMe). With [(η^5-Cp*)Fe$(AN)_3$], **80** enters the stacking reaction to yield [{(η^5-Cp*)Fe}$_2$(μ-η^6-C_5H_5BMe)]PF_6 (93JOM(459)1, 97MI1), with [(η^5-Cp*)Ru$(AN)_3$](CF_3SO_3) [(η^5-Cp*Fe(μ-η^6-C_5H_5BMe)Ru(η^5-Cp*)](CF_3SO_3). Another example of triple deckers includes [(η^5-Cp*)Fe(μ-η^6-C_5H_5BMe)Rh(η^5-Cp*)]$(CF_3SO_3)_2$.



80 **81** **82** **83** **84**

1-Methylboratanaphthalene with [(η^5-Cp*)RuCl]$_4$ gives a traditional $\eta^6(\pi)$-coordinated complex **85** (99OM466). However, 1-boratanaphthalene containing the NPr^i_2-substituent at the heteroatom gives with [(η^5-Cp*)$ZrCl_3$] complex **86**, where the coordination mode decreased from η^6 to η^3 due to the electron-deficient nature of the zirconium(IV) centre. This decrease is more pronounced than that described above for a similar boratabenzene Zr(IV) species. For the product of interaction of the lithium salt of boratanaphthalene and iron(II) chloride, **87**, the structural analysis reveals the η^5-coordination mode (88JOM(343)1).

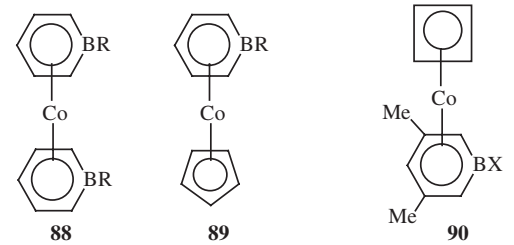


85 **86** **87**

F. Complexes of the Cobalt Group

Sandwich [Co(η^5-Cp)$_2$] on interaction with RBX_2 (R = Ph, Me; X = Cl, Br) gives complexes **88** (R = Ph, Me) and **89** (R = Ph, Me) with the η^6-coordination of boratabenzene ring (71JCS(CC)1328, 72CB3413, 86ADOC199). Complexes **88** are converted into the potassium and sodium salts of boratabenzene on interaction with potassium and sodium cyanide (75AGE184). The latter (R = Ph) reacts with the dimer [(η^4-cod)Rh(Cl)]$_2$ to yield [(η^4-cod)Rh(η^6-C_5H_5BPh)]. Complex **88** with R = OMe (72CB3424) can be prepared similarly. Analogous iron complexes can be prepared starting with cobalt precursors (74CB3780). Another route to these

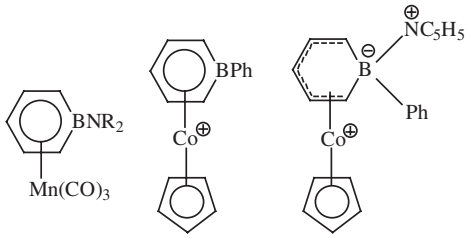
chromium and manganese species is the reaction of 1-substituted boratabenzenes with relevant transition metal chlorides (71JA1804, 73AGE764, 75JA6865, 77CB816). The 6π-electron nature of the boratabenzene anions accounts for the sandwich formation (70AGE805, 72CB3424, 75JCS(D)985). Calculations show that this type of ligand reveals intermediate electronic characteristics between η^5-Cp and η^6-C_6H_6 sandwich-forming ligands (79IC513). Sandwiches $\left[\left(\eta^4\text{-}C_4R'_4\right)Co\left(\eta^6\text{-}C_5H_5BR\right)\right]$ (R = Me, Ph; R′ = H, Me) are also known (83JOM(241)1, 85JOM(280)147). [Li(TMEDA)(3,5-$Me_2C_5H_3BNMe_2$)] reacts with [(η^4-C_4Me_4)Co(AN)$_3$](PF_6) to give sandwich **90** (X = NMe_2) (02EJIC43). Complex **90** (R = NMe_2) enters numerous nucleophilic substitutions at the boron heteroatom. Thus, in refluxing methanol **90** (X = OMe) is formed. The latter with methyl lithium forms **90** (X = Me) and with boron trichloride **90** (X = Cl). The B–Cl derivative when reacted with di-*iso*-butylaluminium hydride gives **73** (X = H), with thallium fluoride – **90** (X = F), and with $LiSnMe_3$ **90** (X = $SnMe_3$). On contact of **90** (X = $SnMe_3$) with air, the dinuclear **91** is formed. The amino complex **90** (X = NMe_2) is quarternized by iodomethane to give **92**. The latter reacts with tetra-*n*-butylammonium cyanide to give **90** (X = CN).



Compound [(Et_3P)$_3$Ir(3,5-$Me_2C_5H_3BF$)](BF_4)$_2$ is made from boron trifluoride and the relevant iridium precursor (97OM606). The BBr_2-derivative of ferrocenyl on reaction with [(η^5-Cp)$_2$Co] produces (1-ferrocenyl-η^6-boratabenzene)(η^5-cyclopentadienyl)cobalt (70AGE805, 72CB3413). Further oxidation with iron(III) chloride gives the cobalt(1+) monocationic species (75JCS(D)985, 96IC7863). Bis(η^6-boratabenzene)cobalt and other similar species (93OM2660) are also known.

Boratabenzenes are the aromatic anionic 6π-electron ligands isoelectronic with the cyclopentadienyl anion (84HCA1616, 85AGE248, 96JA6329, 96JA8176, 96OM1315, 96OM2707). A peculiarity of boratabenzenes, however, is the ability of the boron atom as the Lewis acidic site to attract substituents, in particular nitrogen-containing groups, which can alter the traditional η^6-coordination function (96OM387). Thus,

complex **93** appears to be distorted and appears to be η^5-coordinated due to the strong B–N π-bonding (96JA2291). Another illustration of the $\eta^6 \rightarrow \eta^5$ change is the reaction of complex **94** with pyridine to provide **95** (79CB607).

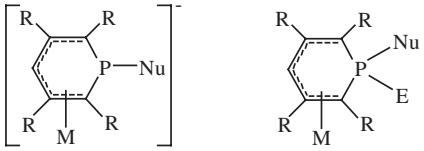


93 **94** **95**

II. P- (As-, Sb-) Analogues

A. Introduction

Electronic properties of phospha-, arsa-, and stibabenzene allow interpretation of the peculiarities of their coordination modes compared to those of unsubstituted pyridine (66AGE846, 70JCP2679, 71JA3293, 71JA6690, 72AGE924, 72JA7596, 73JA928, 74MP601, 75CP345, 76HCA1944, 76TL411, 76TL415, 78ACR153, 82CUZ139, 82JA425, 82MI1, 82TCC125, 90MI1, 92RHC1, 94HA131, 96MI1, 99JOC5524). Phosphinine and arsinine are highly aromatic (82JA5693). Phosphinines as π-ligands are possible catalysts (96JCS(CC)2071). The ligands C_5H_5E (E = N, P, As, Sb) (98OM4417) or substituted derivatives (81JCS(D)1938, 95AGE198, 95AGE2227, 95JCS(D)1873, 96CB263, 96JA7630, 96OM2713, 97JCS(P1)2681, 98EJIC119, 01MI1, 01PIC455) are ambidentate and present the case of η^1(E) vs. $\eta^6(\pi)$ competitive coordination. The η^5-coordinated complexes excluding the phosphorus heteroatom may be prepared in two steps: a preliminary nucleophilic attack at the heteroatom to yield **96** and a subsequent electrophilic quench with the η^5-coordinated product **97** (03EJIC687, 03OM1960).

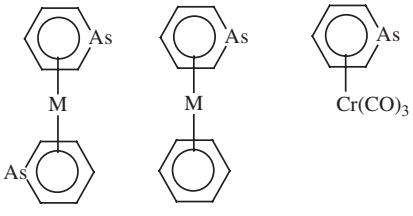


96 **97**

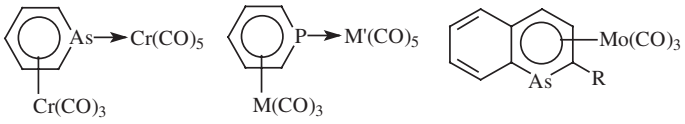
B. Complexes of the Titanium, Vanadium, Chromium, and Manganese Groups

Arsinine in metal–ligand vapour co-condensation reactions yields a series of sandwiches **98** (M = Ti, V, Cr) (86AGE571, 88CB1983, 91AGE547, 99OM1495).

The three-component co-condensation of arsinine, benzene, and chromium gives a mixture of **98** (M = Cr), **99**, and [Cr(η^6-C_6H_6)$_2$] (99OM1495). Arsinine and chromium hexacarbonyl on thermolysis give **100**, and on further treatment with [(η^2-COE)Cr(CO)$_5$] – the η^6 : η^1(As) **101**. Similar species have the structure **102** (M = Cr, Mo; M′ = Cr, Mo, W) (78JOM(148)C31). Arsanaphthalene reacts with [(py)$_3$Mo(-CO)$_3$] in the presence of $Et_2O \cdot BF_3$ to yield the η^6-coordinated products **103** (R = H, $SiMe_3$) (01OM2109).

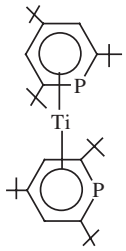


98 **99** **100**



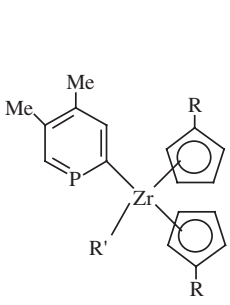
101 **102** **103**

For the homoleptic complexes both situations are realized, e.g. [Ti(η^6-C_5H_5As)$_2$], [V(η^6-C_5H_5E)$_2$] (E = P, As) (91AGE547), and [Cr(η^6-C_5H_5As)$_2$] (86AGE571) but [Cr(η^1-C_5H_5P)$_6$] (93JOM(459)157) and [Cr(η^6-2,4,6-^{t}Bu$_3$$C_5H_2P$)$_2$] upon steric blocking of the *ortho*-positions (85JOM(282)233), and finally [Ni(η^1-C_5H_5P)$_4$] (92AGE1343). Phosphinine with bis(2,4-dimethyl-η^5-pentadienyl)iron gives [(η^1-C_5H_5P)$_5$Fe] (94JA6217). Heteroarenes C_5H_4E (E = P, As, Sb, Bi) tend to form both η^1(E) and η^6(P)-organotransition metal complexes (70TL4941, 74JCS(F2)1222, 82TCC125, 87NJC585, 88JA4204). Phosphinine predominantly forms the $\eta^6(\pi)$-coordinated organotransition metal complexes, especially when the phosphorus heteroatom is sterically screened by the *ortho*-substituents of sufficient bulk, e.g. [V(η^6-PC_5H_2^{t}Bu$_3$-2,4,6)$_2$] (93OM3373). The same reaction was conducted with chromium vapours. 2,4,6-Tri-*tert*-butylphosphinine in the vapour-phase synthesis with titanium vapours produces **104** (97JOM(528)77).



104

2-Bromo-4,5-dimethylphosphinine with $[Zr(C_5H_4R)_2]$ (R = H, Me, $SiMe_3$) gives the η^1(C)-coordinated 2-phosphininyl complexes **105** (R = H, Me, $SiMe_3$; R′ = Br). The latter with methyllithium form **106** (R = H, Me, $SiMe_3$; R′ = Me), which on thermolysis yield the η^2-phosphabenzyne – zirconocene dimers **106** (R = H, Me, $SiMe_3$) (93JCS(CC)789, 94JCS(CC)2065, 97JA9417). Thermolysis of **106** (R = Me) in acetonitrile is an insertion reaction whose product is **107**. The same type of process occurs when **106** (R = H) is reacted with $PhC{\equiv}CPPh_2$ to yield **108**, and with $HC{\equiv}CsiMe_3$ to afford **109**. Insertion into the C_2–Zr bond occurs on interaction of **108** (R = Me) with aldehydes RCHO [R = (η^5-Cp)Fe(η^5-C_5H_4), thienyl] when species **110** [R = (η^5-Cp)Fe(η^5-C_5H_4), thienyl] are formed (97JA9417). With (+)-camphor, **111** is the product when **106** (R = H) is used.



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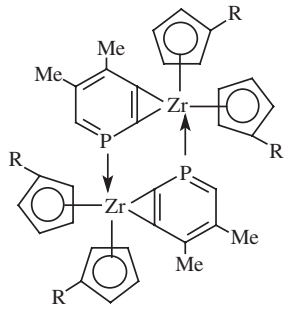

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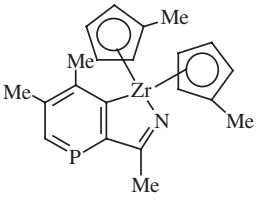

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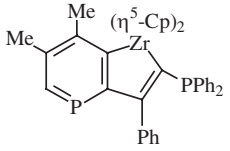

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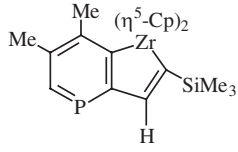

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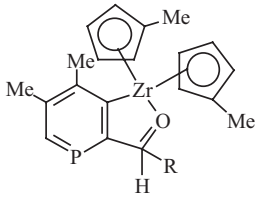

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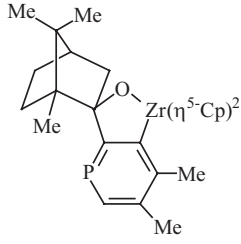
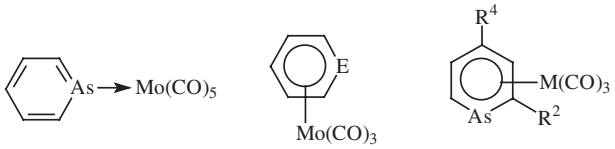


111

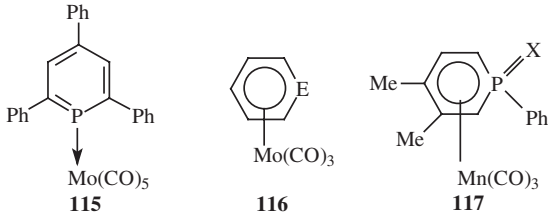
Arsinine with [(η^1-py)$Mo(CO)_5$] in the presence of boron etherate gives the σ-complex **112**, which on pyrolysis can be converted to **113** (E = As) (77JA8099).

However, **113** (E = As) is formed readily from arsabenzene and $Mo(CO)_6$ in diglyme. Stibabenzene with $[(\eta^1\text{-py})_3Mo(CO)_3]$ gives the η^6-coordinated **113** (E = Sb). Arsabenzenes with $[(AN)_3Mo(CO)_3]$ give a series of complexes **114** (R^2 = H, R^4 = Ph, *cyclo*-C_6H_{11}, *t*-Bu, Et, M = Mo; R^2 = Ph, R^4 = Ph, *cyclo*-C_6H_{11}, *t*-Bu, M = Cr, Mo, W) (81JOM(217)333).

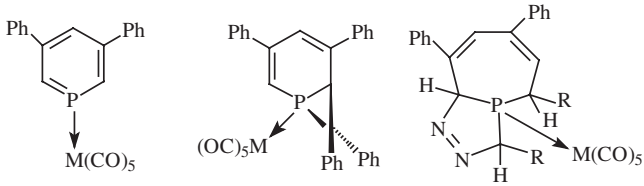


112 **113** **114**

Phosphinines have a much lower basicity than pyridines. Moreover, extensively substituted phosphinines have a negligible basicity (72LHC5, 73FCF1, 75AGE232, 83JOM(257)105). However, 2,4,6-triphenylphosphine forms a series of the η^1(P)-coordinated complexes **115** (73CB2227, 73JOM(49)453) but as π-bases, arsinine and stibinine form the $\eta^6(\pi)$-complexes **116** (E = As, Sb) (70CB2541, 72CB1148, 73CB2222). One of the products of the reaction of phosphinine-1-oxide and sulphide is **117** (X = O, S) (86JOM(305)199). 3,5-Diphenyl-λ^3-phosphinine with molybdenum hexacarbonyl gives the η^1(N)-coordinated **118**, which with phenyldiazomethane forms **119** and with RCH = N_2 **120** (R = H, Me) (87AGE1134).



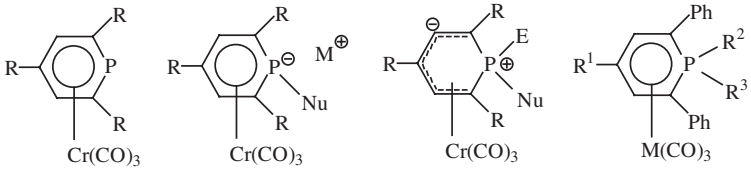
115 **116** **117**



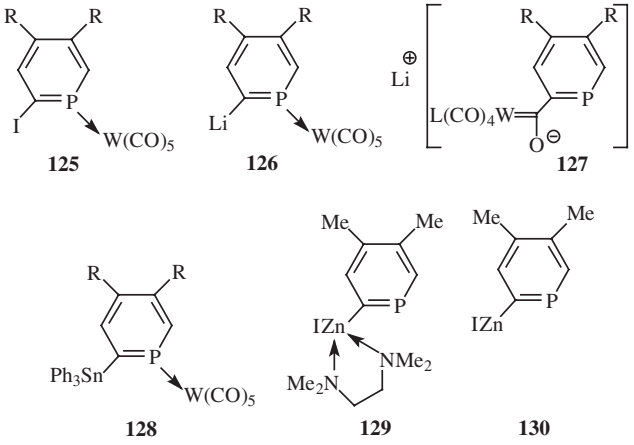
118 **119** **120**

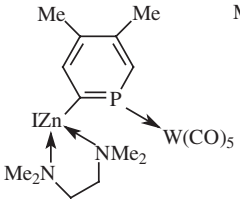
Tricarbonylchromium complexes of 2,4,6-triphenyl- and 2,4,6-tri-*tert*-butyl-λ^3-phosphinines **121** (R = Ph, *t*-Bu) add nucleophiles Li^+Nu^- regio- and stereospecifically at the phosphorus heteroatom at the *exo*-position giving rise to the λ^4-phosphinine anions **122** (R = Ph, *t*-Bu; Nu = Me, Et, Ph, OMe) (83JOM(247)271). The latter add electrophiles (EX) to the *endo*-positions to yield the phosphinine ylide complexes **123** (R = Ph, *t*-Bu; Nu = Me, Et, Ph, OMe; E = Me, CD_3, Et, H). The λ^5-phosphinines were treated by $[M(CO)_6]$ (M = Cr, Mo, W) to yield complexes **124** (R^1 = Me, *t*-Bu, Ph; R^2 = R^3 = Me, Et, *t*-Bu, OMe, F, Et_2N; M = Cr, Mo, W) (76AGE503, 81PS285, 83JOM(257)275). The η^6-coordination is

confirmed by the structural analysis of **124** (R^1 = Ph, $R^2 = R^3$ = OMe, F) (76AGE503).



2-Iodophosphinines when reacted with [(AN)W(CO)$_5$] forms the η^1(P)-coordinated **125** (R = H, Me) (89TL817). Although phosphinines are typical precursors of the η^6-complexes (70CB2541) due to the enhanced electron–acceptor complexes of phosphinine relative to the benzene ring (91AGE547), such a reaction course is not the case for 2-iodophosphinines (96OM794). Complexes **125** (R = H, Me) are lithiated at the 2 position to yield **126** (R = H, Me), which on elevation of the temperature in THF or in an atmosphere of carbon monoxide rearrange to **127** (R = H, Me; L = THF, CO). On interaction with triphenyltin chloride, complexes **126** (R = H, Me) give **128** (R = H, Me). 2-Iodo-4,5-dimethylphosphinine with zinc in the presence of TMEDA in THF medium gives the η^1(C)-coordinated **129** and in DMF it readily gives **130**. Complex **130** reacts with [(AN)Cr(CO)$_5$] to give **131**, which gradually decomposes into **132**. 2-Iodo-4,5-dimethylphosphinine and its organometallic derivatives have an interesting reactivity pattern (92BSCB609, 92TL3537, 93PAC621, 93PS75). Thus, complex **129** with arsenic trichloride gives **133** (96OM802), while **131** under these conditions yields a mixture of products **132**, **133**, **134** and **135**. An interesting chain of transformations takes place between **131** and dimethylchlorostannane and then [(AN)W(CO)$_5$] forming species **136**. Complex **128** with [Cu(CN)(LiCl)$_2$] gives the product of transmetallation **137** and with $AgNO_3$ **138** forms where L is perhaps a solvent, although for silver the η^1(P)-coordination has so far been universal (75TL541). Finally, complexes **129** and **130** with mercury(II) chloride form **139**, and **131** with mercury(II) chloride affords **140**.





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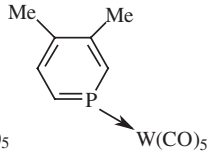

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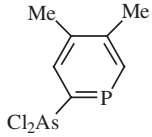

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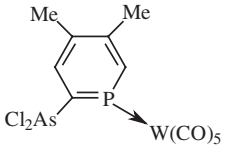

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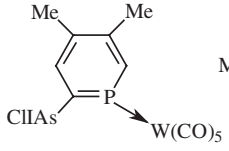

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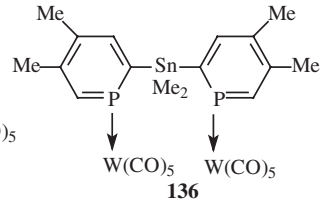

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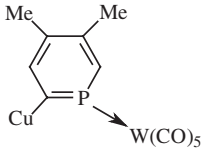

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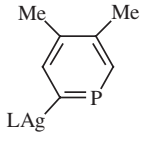

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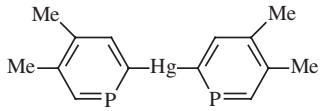

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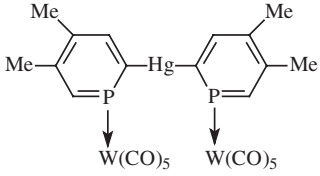
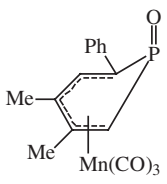


140

C. Complexes of the Manganese, Iron, and Cobalt Groups

4,5-Dimethyl-1,2-diphenyl-1,6-dihydrophosphine sulfide(L) with $[Mn_2(CO)_{10}]$ gives $[Mn_2(CO)_9L]$ and **141** (87JOM(318)83). Heating the first of them gives the η^1(P)-coordinated species **142**.



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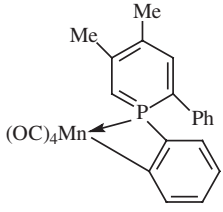
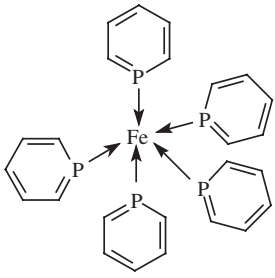


142

Phosphinines and arsinines are ambidentate ligands preferably coordinating via the η^1(P)- or $\eta^6(\pi)$-route (93ZN(B)1581, 98CCR(179)771, 98MI2). Annulated phosphabenzenes are also aromatic (02JOM(643)39). The η^6-mode predominates for the complexes of early transition metals. To ensure the η^6-mode for the Group VI metal complexes, it would be preferable to use the *ortho*-disubstituted phosphinines. The manganese and iron groups offer numerous cases of competitive coordination (79AX(B)1686, 80JOM(187)277), e.g. complexes **143–145** (86OM877). The reaction of 2,4,6-triphenylphosphinine with ferrocene and $AlCl_3$ gives **145**. Then hydrolysis by water yields **146** and further reduction by trichlorosilane produces the η^5-coordinated species **147** (88JOM(343)1). 2-Bromo-4,5-dimethylphosphinine with [(η^5-Cp*)Ru(η^4-$C_6H_{10}Cl$)] and silver tetrafluoroborate gives **148** (01OM3304) along with **149** and **150**. 2,6-Bis(trimethylsilyl)phosphinines with the same precursor gave the η^6-coordinated species **151** ($R_1 = R_2 = R_3 = H$; $R_1 = R_3 = Me$, $R_2 = H$; $R_1 = R_2 = Me$, $R_3 = H$; $R_1 = R_3 = SiMe_3$, $R_2 = H$). Reaction of phosphinine-1-oxide with [(η^5-Cp)Fe$(CO)_2]_2$ gives **152** (R = H) (86JOM(305)199). Treatment of this complex with *n*-butyl lithium leads to the substitution of the P–Ph groups with P-*n*-Bu, and acetylation by MeCOCl–$AlCl_3$ gives the acetyl derivative **152** (R = COMe). Phosphinine-1-oxide with ferrocene gives the η^5-coordinated **153**. Acetylation of the latter occurs via the cyclopentadienyl ring.



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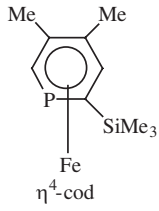

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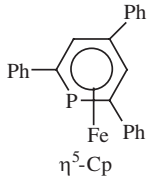

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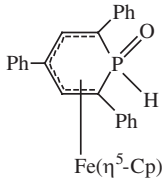

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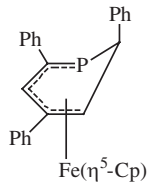

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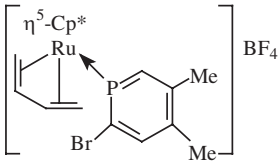

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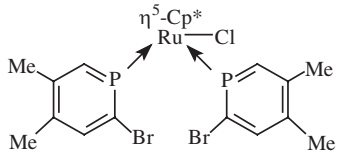

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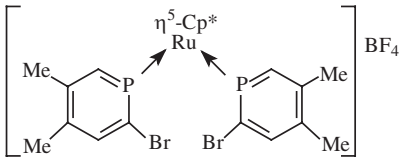

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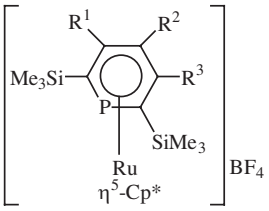

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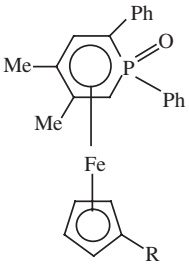

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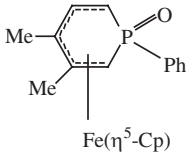
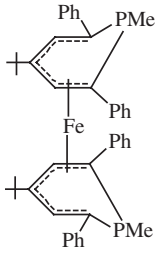


153

Methylated phosphinines with $FeCl_2$ give the bis-η^5-sandwiches **154** (87JOM(318)157). 2-Trimethylsilyl-4,5-dimethylphosphinine with $[(\eta^4\text{-cod})_2Fe]$ gives sandwich **155** (72AGE408, 85OM1565, 85OM1572, 96PSS173). Such a reaction course becomes possible only if the phosphorus atom is sterically blocked by a bulky trimethylsilyl group. The other possibility is preliminary complexation via the heteroatom. 2-Chloro-4,5-dimethylphosphinine with $[Cr(CO)_5(THF)]$ gives **156**, which on further interaction with $[Fe(\eta^4\text{-cod})_2]$ gives **157**.



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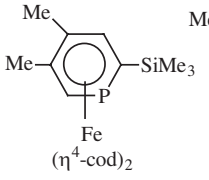

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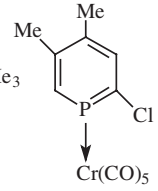

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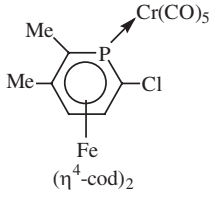
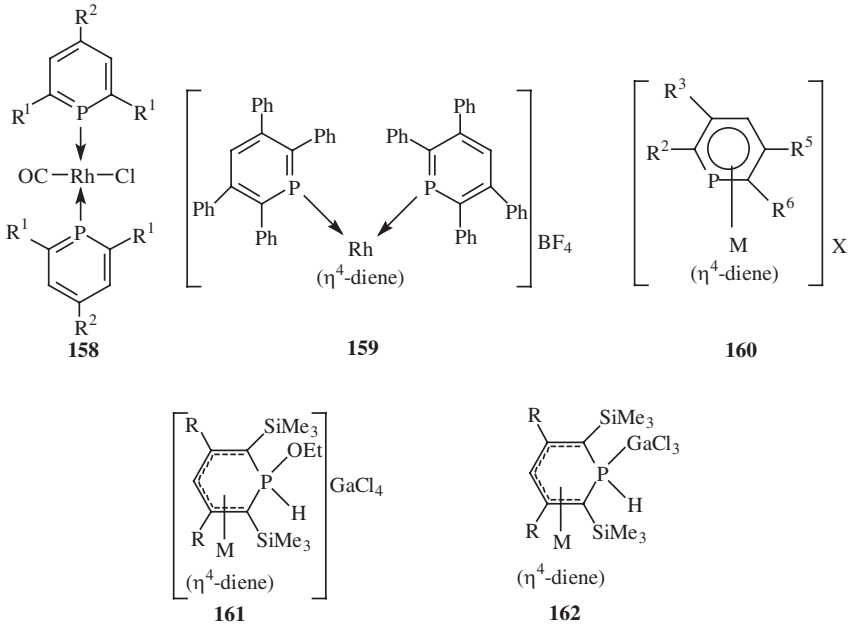


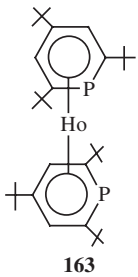
157

A series of phosphabenzenes with the rhodium(I) dimer $[Rh(CO)_2Cl]_2$ gives the η^1(P)-coordinated species **158** [R^1 = Me, R^2 = Ph; $R^1 = R^2$ = Ph; R^1 = 2-naphthyl, R^2 = Ph; R^1 = Ph, $R^2 = C_6H_4$(*p*-OMe); R^1 = Ph, $R^2 = C_6H_4$(*p*-CF_3)] (01EJIC3106) exerting catalytic action in the hydroformylation of olefins. 2,3,5,6-Tetraphenylphosphinine with $[(\eta^4\text{-cod})_2Rh](BF_4)$ gives the η^1(P)-coordinated complex **159** (03EJIC687). 2-Triemthylsilyl-5,6-diphenylphosphinine with $[(\eta^4\text{-cod})RhCl]_2$ gives the same type of product, but with $[(\eta^4\text{-cod})_2Rh](BF_4)$ gives predominantly the η^6-coordinated species **160** (M = Rh, $R^2 = SiMe_3$, R^3 = H, $R^5 = R^6$ = Ph, X = BF_4). 2,6-Bis(trimethylsilyl)phosphinines produce **160** (M = Rh, $R^2 = R^6 = SiMe_3$, $R^3 = R^5$ = Me, Ph, diene = cod, nbd; M = Ir, $R^2 = R^6 = SiMe_3$, $R^3 = R^5$ = Me, Ph, diene = cod, X = BF_4, $GaCl_4$). In ethanol and water complexes **160**

(M = Rh, $R^2 = R^6 = SiMe_3$, $R^3 = R^5$ = Me, Ph, diene = cod, nbd; M = Ir, $R^2 = R^6 = SiMe_3$, $R^3 = R^5$ = Me, diene = cod) transform into **161** (M = Rh, Ir; R = Ph, Me) and **162** (M = Rh, R = Me, Ph; M = Ir, R = Me).



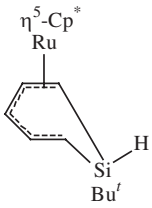
Phosphinines (91AGE547), especially those where the heteroatom is crowded by bulky groups (81LAC1139, 89OM2804, 91JMS(T)231), tend to form the $\eta^6(\pi)$-complexes of the arene type. Thus, 2,4,6-tri-*tert*-butylphosphinine with holmium vapour gives sandwich **163** (97JCS(CC)481).



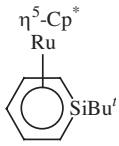
III. Si- (Ge-) Analogues

Silabenzene is characterized by aromatic stabilization and heavily substituted derivatives might have a ligand potential (80TL1405, 82AGE221, 84JOM(271)145, 85CRV419, 89MI1, 89MI2, 96ADOC71, 98MI1, 99PAC495, 00OM1477, 00OM2208). Although aromatic, it is extremely reactive. For the stabilization of silabenzene, Lewis base coordination to the silicon site (88AGE963) or introduction

of the sterically bulky substituents at positions 2 and 6 of the heteroring (00JA5648) can be used. A first report on a η^6-coordinated silabenzene has refered to the analysis of the mass spectrum of [(η^5-4-cyclohexyl-1, 1-dimethylsilacyclohexadienyl) $Fe(CO)_3]^{+\bullet}$ (79JOM(165)399). Later [$Fe(\eta^5\text{-}C_5H_5SiMe_2)_2$] was described (97JCS(CC)997). Compound 1-*t*-butylsilacyclohexadiene was first reacted with *n*-butyllithium and then [{(η^5-Cp*)RuCl}$_4$] or [{(η^5-Cp*)Ru(OMe)}$_2$] to yield the η^5--coordinated silacyclohexadienyl ruthenium sandwich **164** (01OM1195). Using $B(C_6F_5)_3$, the proton at the silicon heteroatom was eliminated and the desired η^6-coordinated silabenzene cationic complex **165** was isolated.

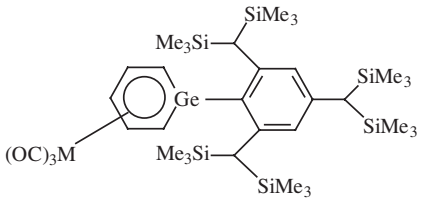


164



165

Silabenzene, 2-silanaphthalene or 9-silaanthracene, as well as germabenzene (82AGE221, 00BCSJ2157, 02OM256) and germanaphthalene are aromatic systems, which can be stabilized and isolated when the protecting group 2,4,6-tris[bis(trimethylsilyl)methylphenyl] is used (97JA6951, 99JA11336, 00AGE634, 00JA5648, 01OM5507, 02CL818, 03OM481). Germabenzene bearing the 1-2,4,6-tris[bis(trimethylsilyl)methyl]phenyl group (02JA6914) is essentially sterically protected to form the η^6-complexes. It enters the ligand exchange reaction with $[M(CO)_3(AN)_3]$ to yield **166** (M = Cr, Mo) (03AGE115).



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IV. Conclusions

1. The dominant coordination mode of boratabenzene is $\eta^6(\pi)$, although deviations from the common situation often occur. It can be an η^1(B) function, a bridging μ-η^6 : η^6 mode, an η^3(NBC) moiety including the exocyclic amino substituent, and an $\eta^5(C_5)$ framework associated with catalytic effects. A new trend is triple-decker complex formation in the chemistry of the Group VIII metals.
2. Phosphinines, arsinines, and stibinines in sharp contrast to pyridines are ambidentate ligands, where $\eta^6(\pi)$ and η^1(E) coordination modes and their combination are common. The role of the $\eta^6(\pi)$ function increases when the

heteroatom is blocked by adjacent bulky substituents. The other possible mode is $\eta^5(C_5)$ excluding the heteroatom. Cases of the η^1(C) and η^2(CC) coordination are known.

3. Silabenzene needs extra stabilization, e.g. by Lewis base coordination to the silicon heteroatom or heavy substitution of the heteroring in order to reveal its $\eta^6(\pi)$ function in sandwich complexes. The process should go via the $\eta^5(C_5)$ species. The same trends are observed for germabenzenes.

References

66AGE846 G. Markl, *Angew. Chem., Int. Ed.*, **5**, 846 (1966).

69CB607 G. E. Herberich, C. Engelke, and W. Pahlmann, *Chem. Ber.*, **112**, 607 (1969).

70AGE805 G. E. Herberich, G. Greiss, and H. F. Heil, *Angew. Chem., Int. Ed.*, **9**, 805 (1970).

70CB2541 J. Deberitz and H. Noth, *Chem. Ber.*, **103**, 2541 (1970).

70JCP2679 W. J. Hehre, R. Ditchfield, R. F. Stewart, and J. A. Pople, *J. Chem. Phys.*, **52**, 2679 (1970).

70TL4941 H. Oehling and A. Schweig, *Tetrahedron Lett.*, 4941 (1970).

71JA1804 A. J. Ashe and P. Shu, *J. Am. Chem. Soc.*, **93**, 1804 (1971).

71JA3293 A. J. Ashe, *J. Am. Chem. Soc.*, **93**, 3293 (1971).

71JA6690 A. J. Ashe, *J. Am. Chem. Soc.*, **93**, 6690 (1971).

71JCS(CC)1328 G. E. Herberich, G. Greiss, H. F. Heil, and J. Muller, *J. Chem. Soc., Chem. Commun.*, 1328 (1971).

72AGE408 G. Markl and C. Matrin, *Angew. Chem., Int. Ed.*, **13**, 408 (1972).

72AGE924 W. Schafer, A. Schweig, F. Bickelhaupt, and H. Veroneer, *Angew. Chem., Int. Ed.*, **11**, 924 (1972).

72CB1148 H. Vahrenkamp and H. Noth, *Chem. Ber.*, **105**, 1148 (1972).

72CB3413 G. E. Herberich and G. Greiss, *Chem. Ber.*, **105**, 3413 (1972).

72CB3424 G. Huttner, B. Krieg, and W. Gartzke, *Chem. Ber.*, **105**, 3424 (1972).

72JA7596 A. J. Ashe and M. D. Gordon, *J. Am. Chem. Soc.*, **94**, 7596 (1972).

72LHC5 G. Markl, *Lect. Heterocycl. Chem.*, **1**, 5 (1972).

73AGE764 G. E. Herberich and H. J. Becker, *Angew. Chem., Int. Ed.*, **12**, 764 (1973).

73CB2222 J. Deberitz and H. Noth, *Chem. Ber.*, **106**, 2222 (1973).

73CB2227 H. Vahrenkamp and H. Noth, *Chem. Ber.*, **106**, 2227 (1973).

73FCF1 K. Dimroth, *Fortschr. Chem. Forsch.*, **38**, 1 (1973).

73JA928 G. Batich, E. Heilbroner, V. Hornig, A. J. Ashe, D. T. Clark, U. T. Cobley, D. Kilcast, and I. Scanlan, *J. Am. Chem. Soc.*, **95**, 928 (1973).

73JOM(49)453 J. Deberitz and H. Noth, *J. Organomet. Chem.*, **49**, 453 (1973).

74CB3780 G. E. Herberich, H. J. Becker, and G. Greiss, *Chem. Ber.*, **107**, 3780 (1974).

74CB3786 G. Huttner and W. Gartzke, *Chem. Ber.*, **107**, 3786 (1974).

74JCS(F2)1222 D. T. Clark and I. T. Scanlan, *J. Chem. Soc., Faraday Trans. II*, **70**, 1222 (1974).

74MP601 F. Gerson, G. Plattner, A. J. Ashe, and G. Markl, *Mol. Phys.*, **28**, 601 (1974).

75AGE184 G. E. Herberich and H. J. Becker, *Angew. Chem., Int. Ed.*, **14**, 184 (1975).

75AGE232 P. Jutzi, *Angew. Chem., Int. Ed.*, **14**, 232 (1975).
75CP345 W. von Niessen, G. H. F. Dierksen, and L. S. Cederbaum, *Chem. Phys.*, **10**, 345 (1975).
75JA6865 A. J. Ashe, E. Meyers, P. Shu, T. Lehmann, and J. Bastide, *J. Am. Chem. Soc.*, **97**, 6865 (1975).
75JCS(D)985 G. E. Herberich, T. Lundt, and J. B. Raynor, *J. Chem. Soc. Dalton Trans.*, 985 (1975).
75TL541 H. Kanter and K. Dimroth, *Tetrahedron Lett.*, 541 (1975).
76AGE503 M. Luckoff and K. Dimroth, *Angew. Chem., Int. Ed.*, **15**, 503 (1976).
76CB2382 G. E. Herberich, H. J. Becker, K. Carsten, C. Engelke, and W. Koch, *Chem. Ber.*, **109**, 2382 (1976).
76HCA1944 A. J. Ashe, F. Surger, M. Y. El-Sheik, E. Heilbroner, J. P. Maier, and J. F. Muller, *Helv. Chim. Acta*, **59**, 1944 (1976).
76TL411 J. Bastide, E. Heilbroner, J. P. Maier, and A. J. Ashe, *Tetrahedron Lett.*, 411 (1976).
76TL415 A. J. Ashe, *Tetrahedron Lett.*, 415 (1976).
77CB816 G. E. Herberich and W. Koch, *Chem. Ber.*, **110**, 816 (1977).
77CB1167 G. E. Herberich and W. Koch, *Chem. Ber.*, **110**, 1167 (1977).
77JA8099 A. J. Ashe and J. C. Colburn, *J. Am. Chem. Soc.*, **99**, 8099 (1977).
78ACR153 A. J. Ashe, *Acc. Chem. Res.*, **11**, 153 (1978).
78JOM(148)C31 K. C. Nainan and C. T. Sears, *J. Organomet. Chem.*, **148**, C31 (1978).
78JOM(153)265 G. E. Herberich, H. J. Becker, and C. Engelke, *J. Organomet. Chem.*, **153**, 265 (1978).
78JOM(157)327 U. Koelle, *J. Organomet. Chem.*, **157**, 327 (1978).
78JOM(160)17 G. E. Herberich, W. Koch, and H. Lueken, *J. Organomet. Chem.*, **160**, 17 (1978).
79AX(B)1686 J. Fischer, A. De Cian, and F. Nief, *Acta Cryst., B*, **35**, 1686 (1979).
79CB607 G. E. Herberich, C. Engelke, and W. Pahlmann, *Chem. Ber.*, **112**, 607 (1979).
79IC513 D. W. Clack and K. D. Warren, *Inorg. Chem.*, **18**, 513 (1979).
79JA7066 A. J. Ashe, W. Butler, and H. F. Sanford, *J. Am. Chem. Soc.*, **101**, 7066 (1979).
79JOM(165)399 G. Markl, C. Soper, P. Hofmeister, and H. Baier, *J. Organomet. Chem.*, **165**, 399 (1979).
80JOM(187)277 F. Nief, C. Charrier, F. Mathey, and M. Simalty, *J. Organomet. Chem.*, **187**, 277 (1980).
80TL1405 G. Markl and D. Rudnik, *Tetrahedron Lett.*, **21**, 1405 (1980).
81JCS(D)1938 F. G. N. Cloke and M. L. H. Green, *J. Chem. Soc., Dalton Trans.*, 1938 (1981).
81JOM(207)345 G. Marr and B. W. Rockett, *J. Organomet. Chem.*, **207**, 345 (1981).
81JOM(208)183 D. W. Clack and K. D. Warren, *J. Organomet. Chem.*, **208**, 183 (1981).
81JOM(217)333 G. Markl, H. Baier, A. Liebl, and K. K. Mayer, *J. Organomet. Chem.*, **217**, 333 (1981).
81LAC1139 H. Lemkuhl, R. Paul, and R. Mynott, *Liebigs Ann. Chem.*, 1139 (1981).
81PS285 K. Dimroth, M. Lueckhoff, and H. Kaletsch, *Phosphorus Sulfur*, **10**, 285 (1981).
82AGE221 G. Markl, D. Rudmick, R. Schultz, and A. Schweig, *Angew. Chem., Int. Ed.*, **21**, 221 (1982).
82CUZ139 G. Markl, *Chem. Unserer Zeit.*, **16**, 139 (1982).
82JA425 P. D. Burrow, A. J. Ashe, D. J. Belville, and K. D. Jordan, *J. Am. Chem. Soc.*, **104**, 425 (1982).

82JA3785 J. M. Schulman, R. L. Disch, and M. L. Sabio, *J. Am. Chem. Soc.*, **104**, 3785 (1982).

82JA5693 A. J. Ashe, T. R. Diephouse, and M. Y. El-Sheikh, *J. Am. Chem. Soc.*, **104**, 5693 (1982).

82MI1 G. E. Herberich, in *"Comprehensive Organometallic Chemistry"* (G. Wilkinson, F. G. A. Stone and E. W. Abel, eds.), Vol. 1, p. 381, Pergamon Press, Oxford (1982).

82TCC125 A. J. Ashe, *Top. Curr. Chem.*, **105**, 125 (1982).

83JOM(241)1 G. E. Herberich and A. K. Naithani, *J. Organomet. Chem.*, **241**, 1 (1983).

83JOM(247)271 K. Dimroth and H. Kaletsch, *J. Organomet. Chem.*, **247**, 271 (1983).

83JOM(254)143 G. E. Herberich and D. Sohnen, *J. Organomet. Chem.*, **254**, 143 (1983).

83JOM(257)105 J. D. Atwood, *J. Organomet. Chem.*, **257**, 105 (1983).

83JOM(257)275 B. W. Rockett and G. Marr, *J. Organomet. Chem.*, **257**, 275 (1983).

84HCA1616 H. Bonnemann, W. Brijoux, R. Brinkmann, and W. Meurers, *Helv. Chim. Acta*, **67**, 1616 (1984).

84JOM(265)225 G. E. Herberich, W. Boveleth, B. Hessner, W. Koch, E. Raabe, and D. Schmitz, *J. Organomet. Chem.*, **265**, 225 (1984).

84JOM(271)145 H. Bock, P. Rosmus, and B. Solouki, *J. Organomet. Chem.*, **271**, 145 (1984).

84ZN(A)678 G. Raube, E. Heyne, W. Schieker, and J. Fleischhauer, *Z. Naturforsch., A*, **39**, 678 (1984).

85AGE248 H. Bonnemann, *Angew. Chem., Int. Ed.*, **24**, 248 (1985).

85CB1644 R. Boese, N. Finke, J. Henkelman, G. Maier, P. Paetzold, H. P. Reisenauer, and G. Schmid, *Chem. Ber.*, **118**, 1644 (1985).

85CRV419 G. Raabe and J. Michl, *Chem. Rev.*, **85**, 419 (1985).

85JOM(280)147 G. E. Herberich, H. J. Becker, B. Hessner, and J. Zelenka, *J. Organomet. Chem.*, **280**, 147 (1985).

85JOM(282)233 A. J. Ashe, W. Buttler, J. C. Colburn, and S. Abu-Orabi, *J. Organomet. Chem.*, **282**, 233 (1985).

85OM1565 T. Dave, S. Berger, E. Bilger, H. Kaletsch, J. Pebler, J. Knecht, and K. Dimroth, *Organometallics*, **4**, 1565 (1985).

85OM1572 G. Baum and W. Massa, *Organometallics*, **4**, 1572 (1985).

85ZN(B)1327 R. Boese, N. Finke, T. Keil, P. Paetzold, and G. Schmid, *Z. Naturforsch., B*, **40**, 1327 (1985).

86ADOC199 G. E. Herberich and H. Ohst, *Adv. Organomet. Chem.*, **25**, 199 (1986).

86AGE571 C. Elschenbroich, J. Kroker, W. Massa, M. Wunsch, and A. J. Ashe, *Angew. Chem., Int. Ed.*, **25**, 571 (1986).

86JOM(305)199 B. W. Rockett and G. Marr, *J. Organomet. Chem.*, **305**, 199 (1986).

86OM877 F. Nief and J. Fischer, *Organometallics*, **5**, 877 (1986).

86ZN(B)167 P. Paetzold, N. Finke, P. Wennek, G. Schmid, and R. Boese, *Z. Naturforsch., B*, **41**, 167 (1986).

87AGE1134 G. Markl, H. J. Beckh, M. L. Ziegler, and B. Nuber, *Angew. Chem., Int. Ed.*, **26**, 1134 (1987).

87JOM(318)83 P. M. Treichel, *J. Organomet. Chem.*, **318**, 83 (1987).

87JOM(318)157 R. C. Kerber, *J. Organomet. Chem.*, **318**, 157 (1987).

87NJC585 F. Mathey, *New J.Chem.*, **11**, 585 (1987).

87ZN(A)352 G. Raube, W. Schleker, E. Heyne, and J. Fleischhauer, *Z. Naturforsch., A*, **42**, 352 (1987).

88AGE295 G. Maier, H. P. Reisenauer, J. Henklemann, and C. Kliche, *Angew. Chem., Int. Ed.*, **27**, 295 (1988).

88AGE963 G. Markl and W. Schlosser, *Angew. Chem., Int. Ed.*, **27**, 963 (1988).

88CB1983 C. Elschenbroich, J. Koch, J. Kroker, M. Wunsch, W. Massa, G. Baum, and G. Stork, *Chem. Ber.*, **121**, 1983 (1988).
88JA4204 K. K. Baldridge and M. S. Gordon, *J. Am. Chem. Soc.*, **110**, 4204 (1988).
88JOM(343)1 R. C. Kerber, *J. Organomet. Chem.*, **343**, 1 (1988).
89MI1 Y. Apeloig, in *"The Chemistry of Organic Silicon Compounds"* (S. Patai and Z. Rappoport, eds.), p. 1015, Wiley, New York (1989).
89MI2 G. Raabe and J. Michl, in *"The Chemistry of Organic Silicon Compounds"* (S. Patai and Z. Rappoport, eds.), Wiley, New York (1989).
89OM733 J. M. Schulman and R. L. Disch, *Organometallics*, **8**, 733 (1989).
89OM2804 A. J. Ashe, J. Michl, J. Waluk, and H. D. Klein, *Organometallics*, **8**, 2804 (1989).
89TL817 P. Le Floch and F. Mathey, *Tetrahedron Lett.*, **30**, 817 (1989).
90CB505 G. Maier, H. J. Wolf, and R. Boese, *Chem. Ber.*, **123**, 505 (1990).
90JA1707 J. Cioslowski and P. J. Hay, *J. Am. Chem. Soc.*, **112**, 1707 (1990).
90MI1 G. Markl, in *"Multiple Bonds and Low Coordination in Phosphorus Chemistry"* (M. Regitz and O. J. Scherer, eds.), p. 220, Thieme, Stuttgart (1990).
91AGE547 C. Elsenbroich, C. Novotny, B. Metz, W. Massa, W. Graulich, K. Biehler, and W. Sauer, *Angew. Chem., Int. Ed.*, **30**, 547 (1991).
91JMS(T)231 H. D. Amberger and J. Ren, *J. Mol. Struct. (THEOCHEM)*, **236**, 231 (1991).
92AGE1343 C. Elschenbroich, M. Novotny, A. Behrendt, W. Massa, and S. Wocaldo, *Angew. Chem., Int. Ed.*, **31**, 1343 (1992).
92BSCB609 H. T. Teunissen and F. Bickelhaupt, *Bull. Soc. Chim. Belg.*, **101**, 609 (1992).
92RHC1 F. Mathey, *Rev. Heteroatom. Chem.*, **6**, 1 (1992).
92TL3537 H. T. Teunissen and F. Bickelhaupt, *Tetrahedron Lett.*, **33**, 3537 (1992).
93JCS(CC)789 P. Le Floch, L. Ricard, and F. Mathey, *J. Chem. Soc., Chem. Commun.*, 789 (1993).
93JOM(450)171 M. R. Churchill and R. F. See, *J. Organomet. Chem.*, **450**, 171 (1993).
93JOM(459)1 G. E. Herberich, U. Englert, and D. Pubans, *J. Organomet. Chem.*, **459**, 1 (1993).
93JOM(459)157 C. Elschenbroich, M. Novotny, J. Kroker, A. Behrendt, W. Massa, and S. Wocaldo, *J. Organomet. Chem.*, **459**, 157 (1993).
93OM2660 G. E. Herberich, W. Klein, and T. P. Spaniol, *Organometallics*, **12**, 2660 (1993).
93OM2891 G. E. Herberich, B. Schmidt, U. Englert, and T. Wagner, *Organometallics*, **12**, 2891 (1993).
93OM3373 C. Elschenbroich, F. Bar, E. Bilger, D. Mahrwald, M. Novotny, and B. Metz, *Organometallics*, **12**, 3373 (1993).
93PAC621 F. Bickelhaupt, *Pure Appl. Chem.*, **65**, 621 (1993).
93PS75 H. T. Teunissen and F. Bickelhaupt, *Phosphorus Sulfur*, **76**, 75 (1993).
93ZN(B)1581 M. Novotny, C. Elschenbroich, A. Behrendt, W. Massa, and S. Wocaldo, *Z. Naturforsch., B*, **48**, 1581 (1993).
94HA131 L. Nyulaszi and G. Keglevich, *Heteroatom Chem.*, **5**, 131 (1994).
94JA6217 C. Elschenbroich, M. Novotny, A. Behrendt, K. Harms, S. Wocaldo, and J. Pebler, *J. Am. Chem. Soc.*, **116**, 6217 (1994).
94JCS(CC)2065 P. Le Floch, A. Kolb, and F. Mathey, *J. Chem. Soc., Chem. Commun.*, 2065 (1994).

94OM619 G. E. Herberich, T. Carstensen, D. P. J. Koffer, M. Klaff, R. Boese, I. Hyla-Krispin, R. Gleiter, M. Stephan, H. Meth, and U. Zenneck, *Organometallics*, **13**, 619 (1994).

95AGE198 D. Bohm, F. Knoch, S. Kummer, U. Schmidt, and U. Zenneck, *Angew. Chem., Int. Ed.*, **34**, 198 (1995).

95AGE2227 P. Binger, S. Leininger, J. Stannek, B. Gabor, R. Mynott, J. Bruckmann, and C. Kruger, *Angew. Chem., Int. Ed.*, **34**, 2227 (1995).

95JA8480 D. Hoic, W. M. Davis, and G. C. Fu, *J. Am. Chem. Soc.*, **117**, 8480 (1995).

95JCS(D)1873 J. Ashmore, J. C. Green, M. L. H. Green, M. L. Smith, C. Mehnert, and E. J. Wucherer, *J. Chem. Soc., Dalton Trans.*, 1873 (1995).

95MI1 G. E. Herberich, in *"Comprehensive Organometallic Chemistry II"* (E. W. Abel, F. G. A. Stone and G. Wilkinson, eds.), Vol. 1, p. 197, Pergamon Press, New York (1995).

95OM471 G. E. Herberich, B. Schmidt, and U. Englert, *Organometallics*, **14**, 471 (1995).

95OM834 G. E. Herberich and U. Jansen, *Organometallics*, **14**, 834 (1995).

96ADOC71 A. G. Brook and M. A. Brook, *Adv. Organomet. Chem.*, **39**, 71 (1996).

96AGE292 H. Noth and M. Schmidt, *Angew. Chem., Int. Ed.*, **35**, 292 (1996).

96CB263 F. Mathey and P. Le Floch, *Chem. Ber.*, **129**, 263 (1996).

96IC7863 U. Hagenau, J. Heck, E. Hendrickx, A. Persoons, T. Schuld, and H. Wong, *Inorg. Chem.*, **35**, 7863 (1996).

96JA2291 G. C. Bazan, G. Rodriguez, A. J. Ashe, S. Al-Ahmad, and C. Muller, *J. Am. Chem. Soc.*, **118**, 2291 (1996).

96JA6329 S. Qiao, D. A. Hoic, and G. C. Fu, *J. Am. Chem. Soc.*, **118**, 6329 (1996).

96JA7630 P. L. Arnold, F. G. N. Cloke, P. B. Hitchcock, and J. F. Nixon, *J. Am. Chem. Soc.*, **118**, 7630 (1996).

96JA8176 D. A. Hoic, W. M. Davis, and G. C. Fu, *J. Am. Chem. Soc.*, **118**, 8176 (1996).

96JA10317 C. M. Kowal and G. C. Bazan, *J. Am. Chem. Soc.*, **118**, 10317 (1996).

96JCS(CC)2071 B. Breit, *J. Chem. Soc. Chem. Commun.*, 2071 (1996).

96MI1 A. J. Ashe, in "*Comprehensive Heterocyclic Chemistry II*" (A. McKillop, Vol. Ed.), Vol. 5, p. 669, Pergamon, Oxford, 1996.

96OM387 A. J. Ashe, J. W. Kampf, C. Muller, and M. Schneider, *Organometallics*, **15**, 387 (1996).

96OM794 H. T. Teunissen and F. Bickelhaupt, *Organometallics*, **15**, 794 (1996).

96OM802 H. T. Teunissen and F. Bickelhaupt, *Organometallics*, **15**, 802 (1996).

96OM1315 D. A. Hoic, J. R. Wolf, W. M. Davis, and G. C. Fu, *Organometallics*, **15**, 1315 (1996).

96OM2707 G. E. Herberich, U. Englert, M. U. Schmidt, and R. Standt, *Organometallics*, **15**, 2707 (1996).

96OM2713 F. Knoch, F. Kremer, U. Schmidt, U. Zenneck, P. Le Floch, and F. Mathey, *Organometallics*, **15**, 2713 (1996).

96OM5236 G. E. Herberich, U. Englert, B. Ganter, and C. Lamertz, *Organometallics*, **15**, 5236 (1996).

96PSS173 D. Bohm, H. Geiger, F. Knoch, F. Kremer, S. Kummer, P. Le Floch, F. Mathey, U. Schmidt, and U. Zenneck, *Phosphorus, Silicon, Sulfur, Relat. Elem.*, **109–110**, 173 (1996).

97AGE267 M. C. Amendola, K. E. Stockman, D. A. Hoic, W. M. Davis, and G. C. Fu, *Angew. Chem., Int. Ed.*, **36**, 267 (1997).

97AGE2014 A. J. Ashe, S. Al-Ahmad, J. W. Kampf, and V. G. Young, *Angew. Chem., Int. Ed.*, **36**, 2014 (1997).
97IJQC441 P. B. Karadakov, M. Ellis, J. Gerratt, D. L. Cooper, and M. Raimondi, *Int. J. Quant. Chem.*, **63**, 441 (1997).
97JA6951 N. Tokitoh, K. Wakita, R. Okazaki, S. Nagase, P. R. Schleyer, and H. Jiao, *J. Am. Chem. Soc.*, **119**, 6951 (1997).
97JA7155 D. A. Hoic, M. DiMare, and G. C. Fu, *J. Am. Chem. Soc.*, **119**, 7155 (1997).
97JA9305 J. S. Rogers, G. C. Bazan, and C. K. Sperry, *J. Am. Chem. Soc.*, **119**, 9305 (1997).
97JA9417 P. Rosa, P. Le Floch, L. Ricard, and F. Mathey, *J. Am. Chem. Soc.*, **119**, 9417 (1997).
97JCS(CC)481 P. L. Arnold, F. G. N. Cloke, and P. B. Hitchcock, *J. Chem. Soc., Chem. Commun.*, 481 (1997).
97JCS(CC)997 B. F. G. Johnson, C. M. Martin, M. Nowotny, W. Palmer, and S. Parsons, *J. Chem. Soc., Chem. Commun.*, 997 (1997).
97JCS(P1)2681 B. Breit, R. Winde, and K. Harms, *J. Chem. Soc., Perkin Trans. 1*, 2681 (1997).
97JOC8286 J. Tweddel, D. A. Hoic, and G. C. Fu, *J. Org. Chem.*, **62**, 8286 (1997).
97JOM(528)77 P. L. Arnold, F. G. N. Cloke, K. Khan, and P. Scott, *J. Organomet. Chem.*, **528**, 77 (1997).
97JOM(535)29 J. T. Park, B. W. Woo, S. C. Yoon, and S. C. Shim, *J. Organomet. Chem.*, **535**, 29 (1997).
97MI1 G. E. Herberich, in *Advances in Boron Chemistry* (W. Siebert, ed.), Royal Soc. Chem., Cambridge, 1997, p. 211.
97OM163 A. J. Ashe, J. W. Kampf, and J. R. Waas, *Organometallics*, **16**, 163 (1997).
97OM606 J. R. Bleeke, R. Behm, Y. F. Xie, M. Y. Chiang, K. D. Robinson, and A. M. Beatty, *Organometallics*, **16**, 606 (1997).
97OM926 G. E. Herberich, J. Rosenplanter, B. Schmidt, and U. Englert, *Organometallics*, **16**, 926 (1997).
97OM1501 S. Qiao, D. A. Hoic, and G. C. Fu, *Organometallics*, **16**, 1501 (1997).
97OM2492 G. C. Bazan, G. Rodriguez, A. J. Ashe, S. Al-Ahmad, and J. W. Kampf, *Organometallics*, **16**, 2492 (1997).
97OM3751 G. E. Herberich, U. Englert, and A. Schmitz, *Organometallics*, **16**, 3751 (1997).
97PSS295 A. J. Ashe, S. Al-Ahmad, and J. W. Kampf, *Phosphorus, Sulfur, Silicon*, **124–125**, 295 (1997).
97ZAAC1098 U. Englert, G. E. Herberich, and J. Rosenplanter, *Z. Anorg. Allg. Chem.*, **623**, 1098 (1997).
98CCR(179)771 P. Le Floch and F. Mathey, *Coord. Chem. Rev.*, **179–180**, 771 (1998).
98EJIC119 P. Le Floch, F. Knoch, F. Kremer, F. Mathey, J. Scholz, W. Scholz, K. H. Thiele, and U. Zenneck, *Eur. J. Inorg. Chem.*, 119 (1998).
98JA1082 R. W. Barnhart, G. C. Bazan, and T. Moure, *J. Am. Chem. Soc.*, **120**, 1082 (1998).
98JA3883 A. J. Ashe, S. Al-Ahmad, X. Fang, and J. W. Kampf, *J. Am. Chem. Soc.*, **120**, 3883 (1998).
98JA6037 R. A. Lee, R. J. Lachicotte, and G. C. Bazan, *J. Am. Chem. Soc.*, **120**, 6037 (1998).
98JA7791 C. K. Sperry, W. D. Cotter, R. A. Lee, R. J. Lachicotte, and G. C. Bazan, *J. Am. Chem. Soc.*, **120**, 7791 (1998).
98MI1 Y. Apeloig and M. Karni, in *"The Chemistry of Organic Silicon Compounds"* (S. Patai and Z. Rappoport, eds.), Vol. 2, Wiley, New York (1998).

98MI2 K. B. Dillon, F. Mathey, in *Phosphorus: the Carbon Copy*, Wiley, Chichester (1998).
98OM1254 G. E. Herberich, B. Ganter, and M. Pons, *Organometallics*, **17**, 1254 (1998).
98OM3883 A. J. Ashe, S. Al-Ahmad, X. Fang, and J. W. Kampf, *Organometallics*, **17**, 3883 (1998).
98OM4417 C. Elschenbroich, S. Voss, O. Schiemann, A. Lipek, and K. Harms, *Organometallics*, **17**, 4417 (1998).
99CSR51 C. Bohm and K. Muniz, *Chem. Soc. Rev.*, **28**, 51 (1999).
99JA1288 J. S. Rogers, R. J. Lachicotte, and G. C. Bazan, *J. Am. Chem. Soc.*, **121**, 1288 (1999).
99JA1513 C. K. Sperry, G. C. Bazan, and W. D. Cotter, *J. Am. Chem. Soc.*, **121**, 1513 (1999).
99JA8112 M. A. Putzer, J. S. Rogers, and G. C. Bazan, *J. Am. Chem. Soc.*, **121**, 8112 (1999).
99JA11336 K. Wakita, N. Tokitoh, R. Okazaki, S. Nagase, P. R. Schleyer, and H. Jiao, *J. Am. Chem. Soc.*, **121**, 11336 (1999).
99JOC5524 G. Fuson, A. Sevin, N. Avarvari, F. Mathey, and P. Le Floch, *J. Org. Chem.*, **64**, 5524 (1999).
99JOM(581)92 A. J. Ashe, S. Al-Ahmad, and X. Fang, *J. Organomet. Chem.*, **581**, 92 (1999).
99OM466 A. J. Ashe, X. Fang, and J. W. Kampf, *Organometallics*, **18**, 466 (1999).
99OM1363 A. J. Ashe, X. Fang, and J. W. Kampf, *Organometallics*, **18**, 1363 (1999).
99OM1495 C. Elschenbroich, J. Kroker, M. Novotny, A. Behrendt, B. Metz, and K. Harms, *Organometallics*, **18**, 1495 (1999).
99OM3406 G. E. Herberich, U. Englert, B. Ganter, M. Pons, and R. Wang, *Organometallics*, **18**, 3406 (1999).
99OM4234 A. J. Ashe, S. Al-Ahmad, and J. W. Kampf, *Organometallics*, **18**, 4234 (1999).
99OM4747 G. E. Herberich, X. Zheng, J. Rosenplanter, and U. Englert, *Organometallics*, **18**, 4747 (1999).
99OM5496 G. E. Herberich, U. Englert, A. Fischer, J. Ni, and A. Schmitz, *Organometallics*, **18**, 5496 (1999).
99PAC495 N. Tokitoh, *Pure Appl. Chem.*, **71**, 495 (1999).
00AGE634 K. Wakita, N. Tokitoh, R. Okazaki, and S. Nagase, *Angew. Chem., Int. Ed.*, **39**, 634 (2000).
00BCSJ2157 K. Wakita, N. Tokitoh, and R. Okazaki, *Bull. Chem. Soc. Jap.*, **73**, 2157 (2000).
00EJIC979 G. E. Herberich, U. Englert, B. Ganter, and M. Pons, *Eur. J. Inorg. Chem.*, 979 (2000).
00IC5579 X. Zheng, U. Englert, G. E. Herberich, and J. Rosenplanter, *Inorg. Chem.*, **39**, 5579 (2000).
00JA730 J. S. Rogers, X. Bu, and G. C. Bazan, *J. Am. Chem. Soc.*, **122**, 730 (2000).
00JA1371 G. C. Bazan, W. D. Cotter, Z. J. A. Komon, R. A. Lee, and R. J. Lachicotte, *J. Am. Chem. Soc.*, **122**, 1371 (2000).
00JA3969 B. Y. Lee, S. Wang, M. Putzer, G. P. Bartholomew, X. Bu, and G. C. Bazan, *J. Am. Chem. Soc.*, **122**, 3969 (2000).
00JA5648 K. Wakita, N. Tokitoh, R. Okazaki, N. Takagi, and S. Nagase, *J. Am. Chem. Soc.*, **122**, 5648 (2000).
00JCS(CC)1209 J. S. Rogers and G. C. Bazan, *J. Chem. Soc., Chem. Commun.*, 1209 (2000).

00OM1477 K. K. Baldridge, O. Uzan, and J. M. L. Martin, *Organometallics*, **19**, 1477 (2000).
00OM2208 E. C. Brown and W. T. Borden, *Organometallics*, **19**, 2208 (2000).
00OM3751 X. Zheng and G. E. Herberich, *Organometallics*, **19**, 3751 (2000).
00OM3948 J. S. Rogers, X. Bu, and G. C. Bazan, *Organometallics*, **19**, 3948 (2000).
01ADOC101 G. C. Fu, *Adv. Organomet. Chem.*, **47**, 101 (2001).
01EJIC3013 X. Zheng and G. E. Herberich, *Eur. J. Inorg. Chem.*, 3013 (2001).
01EJIC3106 B. Breit, R. Winde, T. Mackewitz, R. Paciello, and K. Harms, *Eur. J. Inorg. Chem.*, 3106 (2001).
01IC3117 X. Zheng, B. Wang, U. Englert, and G. E. Herberich, *Inorg. Chem.*, **40**, 3117 (2001).
01JCS(CC)619 D. Woodmansee, X. Bu, and G. C. Bazan, *J. Chem. Soc., Chem. Commun.*, 619 (2001).
01MI1 P. Le Floch, in *"Phosphorus – Carbon Heterocyclic Chemistry: The Role of a New Domain"* (F. Mathey ed.), p. 485, Pergamon, New York (2001).
01OM468 A. J. Ashe, S. Al-Ahmad, X. Fang, and J. W. Kampf, *Organometallics*, **20**, 468 (2001).
01OM1195 J. M. Dysard, T. D. Tilley, and T. K. Woo, *Organometallics*, **20**, 1195 (2001).
01OM2109 A. J. Ashe, X. Fang, and J. W. Kampf, *Organometallics*, **20**, 2109 (2001).
01OM3304 N. Mezailles, L. Ricard, F. Mathey, and P. Le Floch, *Organometallics*, **20**, 3304 (2001).
01OM5507 N. Nakata, N. Takeda, and N. Tokitoh, *Organometallics*, **20**, 5507 (2001).
01PIC455 N. Mezailles, F. Mathey, and P. Le Floch, *Progr. Inorg. Chem.*, **49**, 455 (2001).
02CL818 N. Nakata, N. Takeda, and N. Tokitoh, *Chem. Lett.*, 818 (2002).
02EJIC31 B. Wang, X. Zheng, and G. E. Herberich, *Eur. J. Inorg. Chem.*, 31 (2002).
02EJIC43 G. E. Herberich, T. S. B. Baul, and U. Englert, *Eur. J. Inorg. Chem.*, 43 (2002).
02JA6914 N. Nakata, N. Takeda, and N. Tokitoh, *J. Am. Chem. Soc.*, **124**, 6914 (2002).
02JOM(642)275 B. Y. Lee and G. C. Bazan, *J. Organomet. Chem.*, **642**, 275 (2002).
02JOM(643)39 S. M. Bachrach, *J. Organomet. Chem.*, **643–644**, 39 (2002).
02JOM(649)136 A. R. Kudinov, D. A. Loginov, Z. A. Starikova, and P. V. Petrovskii, *J. Organomet. Chem.*, **649**, 136 (2002).
02OM256 N. Takeda, A. Shinohara, and N. Tokitoh, *Organometallics*, **21**, 256 (2002).
02OM1949 X. Zheng, B. Wang, and G. E. Herberich, *Organometallics*, **21**, 1949 (2002).
02OM3189 Z. J. A. Komon, J. S. Rogers, and G. C. Bazan, *Organometallics*, **21**, 389 (2002).
03AGE115 N. Nakata, N. Takeda, and N. Tokitoh, *Angew. Chem., Int. Ed.*, **42**, 115 (2002).
03AGE4510 X. Fang, D. Woodmansee, X. Bu, and G. C. Bazan, *Angew. Chem., Int. Ed.*, **42**, 4510 (2003).
03CRV283 V. C. Gibson and S. K. Spitzmesser, *Chem. Rev.*, **103**, 283 (2003).
03EJIC687 M. Doux, L. Ricard, F. Mathey, P. Le Floch, and N. Mezailles, *Eur. J. Inorg. Chem.*, 687 (2003).
03EJIC2175 X. Zheng and G. E. Herberich, *Eur. J. Inorg. Chem.*, 2175 (2003).

03OM203 A. J. Ashe, J. W. Kampf, and M. W. Schiester, *Organometallics*, **22**, 203 (2003).

03OM481 N. Nakata, N. Takeda, and N. Tokitoh, *Organometallics*, **22**, 481 (2003).

03OM910 A. J. Ashe, Z. Bajko, M. D. Carr, and J. W. Kampf, *Organometallics*, **22**, 910 (2003).

03OM1960 A. Moores, L. Ricard, P. Le Floch, and N. Mezailles, *Organometallics*, **22**, 1960 (2003).

03OM5496 G. E. Herberich, U. Englert, A. Fischer, J. Ni, and A. Schmitz, *Organometallics*, **18**, 5496 (1999).

Imidazopyridines: 1- and 3-Deazapurines

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Dedicated to the memory of academician A.V. Kirsanov, who with A.E. Chichibabin first synthesized imidazopyridines

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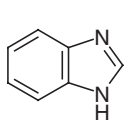
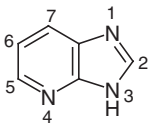
I. Introduction

The subjects of this review are syntheses, chemical and other properties of imidazo[4,5-b]pyridine (IbP) (**1**), imidazo[4,5-c]pyridine (IcP) (**2**) and their derivatives. The practical significance of these compounds is due to their structural and chemical relation to purine (**3**) and benzimidazole (**4**). Purine, known to be among the most important fundamental substances in biology, is responsible, along with pyrimidine, for encoding and transmitting hereditary information (69MI2, 70MI2, 83MI2). Benzimidazole plays an important role in biochemistry and medicine (74CRV279).



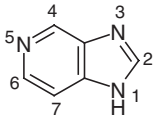
(4)

Benzimidazole



(1)

3H-Imidazo[4,5-b] pyridine or 1-deazapurine



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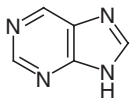
1H-Imidazo[4,5-c] pyridine or 3-deazapurine

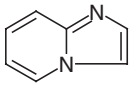


(3)

Purine

Molecules of imidazopyridines **1** and **2** (IP) are built from imidazole and pyridine nuclei that have no common nitrogen atom. This distinguishes imidazopyridines **1** and **2** from imidazo[1,2-a]pyridine **2** and imidazo[1,5-a]pyridine **6**. The latter two have little in common with purine in terms of molecular structure and chemical properties (66JOC1295, 67JOC2430). Consequently, imidazopyridines **5** and **6** are not analogues of purine and are not considered here.

In the current chemical literature, the above-mentioned names for **1** and **2** are adopted. In cases, when it is meant to emphasize the structural relationship with purine, imidazopyridines **1** and **2** are regarded as deazapurines with a numbering of ring atoms that is characteristic for purine. In early works one can also find names for **1** and **2** using the ''a''-nomenclature (79MI3) based on benzimidazole (e.g., 4-azabenzimidazole for the 1-deazapurine) (48JCS1389) or even indene (1,3,5,-triazaindene for the same 1-deazapurine (66JCS(B)285). Such names as imidazo[4′5′:2,3]pyridine (59JCS3157), 1,3,4-imidazopyridine (56JA4130), imidazo(*b*)pyridine (59JOC1455), pyrimidazole (46JPJ31), pyrido[2,3-*d*]imidazole (69RZC573) and spinazol (52AF515) are also found.



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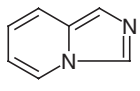

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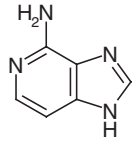
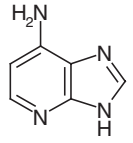


(7)



(8)

The first report by Chichibabin and Kirsanov on the synthesis of imidazopyridines appeared in 1927. They obtained 2-methylimidazo[4,5-b]pyridine and its 5-chloro derivative by heating the corresponding 2,3-diaminopyridines with acetic anhydride (27CB766). After 11 years, Weidenhagen and Weeden described the synthesis of imidazo[4,5-c]pyridine and its 2-substituted derivatives (38CB2347). However, interest in this class of potential biologically active compounds appeared later. It was started by the work of Kogl, van der Want and Salemink, in which they began the synthesis and the study of biological properties of the analogues of natural purine bases (48RTC29). Soon, the inhibiting action on the growth of some microorganisms by the known 3-deazaadenine **7** (52AF515) and, later, by 1-deazaadenine **8** (66B756) was discovered. It was the search for drugs among the derivatives of purine analogues that largely stimulated further work on the synthesis of new substituted imidazopyridines. Here it is important to note that the synthesis of such compounds was mostly based on cyclization by carbon acids (their esters, nitriles, etc.) of *ortho*-diaminopyridines, the necessary substituents being entered in advance (see Section II.A). Much more seldom, the addition of a pyridine ring to imidazole derivatives had been carried out mostly in the synthesis of deazaguanine and deazaguanosine (75JA2916, 76JA1492). Few examples are known for the conversion of other heterocycles into derivatives of imidazopyridines (73JCS(P1)1794, 82JOC167).

When we started our research in the late 1960s, the synthesis of various derivatives of imidazopyridines was seldom studied.

The chemical reactions of imidazopyridines known by the early 1970s related to their substitution reactions at the ring nitrogen atom or to the conversions of substituents (NO_2 into NH_2, NH_2 into OH, OH into CI, CI into SH, CH_3 into COOH, etc.) (48RTC29, 59JOC1455, 69JHC759, 72RTC650). Substitution of hydrogen atoms at the carbon atoms of imidazopyridine was unknown, except for nitration of imidazo[4,5-b]pyridine-4-oxide to its 7-nitro derivative (66IJC403).

The next stage (after 1970s) was associated with the study of their main chemical properties along with an increase in the number of publications on biologically active derivatives of imidazopyridines obtained both by cyclization of diaminopyridines and as a result of entering new substituents into the most accessible derivatives of imidazopyridines.

Nowadays, a large number of variously substituted imidazopyridines are found to possess high biological activity (see Section V).

Two reviews on imidazopyridines are worth mentioning. The review by Lunt on the chemistry of 1- and 3-deazapurines covered them most completely up to the time of its publication (85MI5). However, the concise review of Montgomery and Secrist in the book (84CHEC(5)) contained still more information and references. In a special review on aza- and deazaanalogues of purine nucleosides, the most significant section is dedicated to 1- and 3-deazapurine nucleosides (81KG147).

Some of the IP's properties were reviewed by Rusinov and Chupakhin in a monograph (91MI1).

My review is not intended to provide a complete coverage and analysis of publications on imidazopyridines, but it is aimed to give an idea of the main achievements in this field.

II. Synthesis of the Imidazopyridines

Imidazopyridines (IPs) may be synthesized from pyridine or imidazole derivatives by building up the second ring, and also by ring transformations from the other heterocyclic compounds. However, these methods are not of equal efficiency, and the most important preparative procedures utilize amino derivatives of pyridine as initial compounds for IP's synthesis. The main IP's precursors are *o*-diaminopyridines (*o*-DAP).

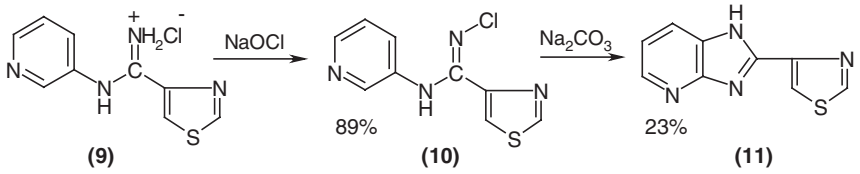
A. Syntheses from Pyridines

1. *Unsubstituted and Substituted Imidazopyridines*

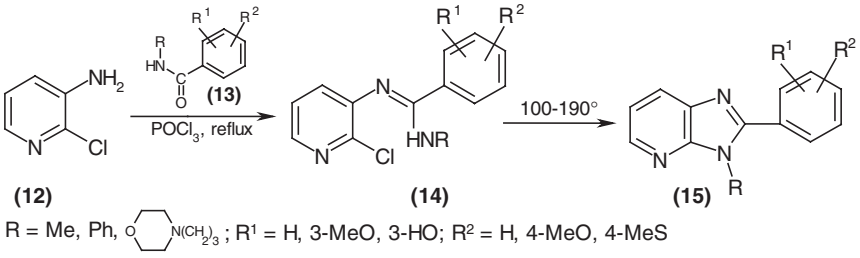
The syntheses of **1** and **2** commonly involve aminopyridine or *o*-diaminopyridine (*o*-DAP) derivatives, the latter being the most important.

The simplest but uncommon procedure for imidazo[4,5-b]pyridine (IbP) derivative **11** from monoaminopyridines involved oxidation of amidine **9** by sodium hypochlorite to give *N*-chloroamidine **10** followed by boiling its methanol-aqueous solution with sodium carbonate.

Amidine of a similar structure obtained from 2-aminopyridine under the same conditions gave triazolopyridine (65JOC259) instead of IP.



2-Chloro-3-aminopyridine **12** (36CB2593) as well as its 2-bromo analogue, when heated with benzamides **13** in $POCl_3$, gave amidines **14** whose cyclization into aryl-substituted imidazo[4,5-b]pyridines (IbP) **15** occurred on heating either in a solvent (ethylene glycol, DMSO, DMF) or in the presence of acids (HCl) or bases (NaOH, NaH, *tert*-C_4H_9OK). However, yield of IPs **15** is poor (from 1.7 to 35%) (78SUP634673).

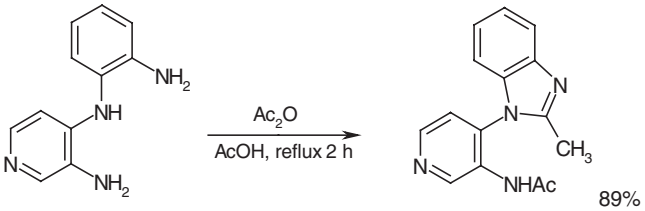


Analogously, a satisfactory yield of IbP was obtained by treating 2,6-dichloro-5-fluoro-3-aminopyridine with substituted acetamide in the presence of oxalyl chloride to give an amidine followed by reaction with potassium carbonate (94HCA1057).

Sometimes, fusing 3-acylamino-2-chloropyridine with anilines (180–250 °C, 15 min) resulted in an exothermic reaction affording 2,3-disubstituted IbP (90MI1) in a high yield.

The classical synthesis of IPs consisted in cyclization of *o*-DAP with carboxylic acids, their derivatives and precursors. This method was used to prepare the majority of IP derivatives with various substituents in the imidazole and pyridine rings. However, it should be mentioned that cyclization of *o*-diaminopyridines with carboxylic acids and their derivatives occurs less readily than that of *o*-phenylenediamines. Whereas the latter are cyclized into benzimidazoles when heated with carboxylic acid for a short time (51CRV397), boiling a 2,3-DAP and an acetic anhydride mixture for 2 h affords only 2,3-diacetylaminopyridine, and fusion of this diamine with benzoic anhydride resulted only in the formation of 2,3-dibenzoylaminopyridine (64JOC3403).

Transformation of triamine **16** into benzimidazole **17** when heated with acetic anhydride (96ZOR586) illustrates that benzimidazole formation is a lot easier than IP's synthesis.

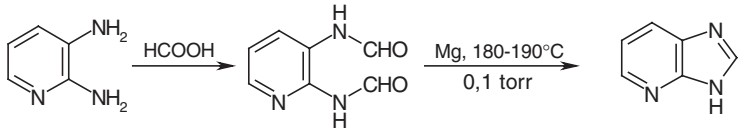


(16) **(17)**

Similarity to the benzimidazole synthesis led sometimes to an erroneous assignment of an imidazopyridine structure to acyl derivatives of *o*-DAPs. Thus, Garmaise and Komlossy (64JOC3403) indicated that Takahashi and Yajima (46JPJ31) believed the products they had prepared by acylation of 2,3-DAP with aromatic acid anhydrydes really had the IP structure. Moreover, it was revealed that the reaction between *o*-DAP and anthranilic acid afforded merely a salt of these compounds.

Korte reported that it was impossible to cyclize 2,3-DAP **18** by boiling with anhydrous formic acid (even on repeated boiling of the residue after acid removal with a fresh acid portion). In this case, only diformyl derivative **19** of diamine **18** formed, whose cyclization into **1** succeeded by vacuum distillation with powdered Mg at 180–190 °C (52CB1012).[1]

[1]The cyclization procedure by means of vacuum distillation of the starting diamine in the presence of powdered Mg had been proposed formerly for the synthesis of 2-methylimidazole from sym-diacetylethylenediamine (46JA1774).



(18) (19) (1)

Gorton and Shive demonstrated that cyclization of *o*-DAP required severe conditions (57JA670). This can be illustrated by an example of 5-amino-7-oxy-IbP preparation from diamine 4-oxy-2,3,6-triaminoPy (HCOOH, refl. 4 h, distillation 270 °C/1 torr).

Knobloch and Kuhne reported the failure of the synthesis of 2-substituted IcP from 3,4-DAPs under the conditions applied to the preparation of the corresponding benzimidazole derivatives. Heating this diamine with carboxylic acids and the respective esters or acyl chlorides resulted either in the recovery of the parent substances or in the formation of their *N*-acylated derivatives (62JPR199). According to the reports by Weidenhagen and Weeden, boiling 3,4-DAP with formic or acetic acids for many hours gave only monoacyl derivatives of the parent diamine (38CB2347). 3,4-Bis(formylamino)pyridine was obtained in high yield by refluxing 3,4-diaminopyridine in excess 100% formic acid (88EUP260613).

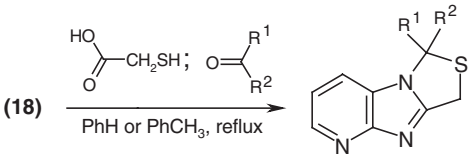
No wonder that the success of the first synthesis of 2-methyl-IbP from diamine **18** carried out by Chicibabin and Kirsanov was ensured by subjecting the residue after boiling the diamine with acetic anhydride and distilling off the acetic acid and anhydride by vacuum distillation (27CB766).

Heating 5-bromo-2,3-diaminoPy with 98% formic acid gives 5-Br-2,3-diformylaminopyridine, whereas reaction between the same diamine with acetic anhydride results in diacetylaminopyridine, which quickly affords IPs (48JCS1389) on heating at 315 °C.

Vacuum distillation, sublimation or heating acyl derivatives of *o*-DAPs at high temperature were often used to prepare IPs (57JA670, 61USP3004978, 64CPB866, 64JOC2611, 66CB244, 77SUP557758, 79CZ387, 86TL5997, 88EUP260613, 89PHA267, 89USP4804658, 90JHC563, 91JMC2993).

It should be noted that fusion of a mixture of *o*-DAP and carboxylic acids at 190–240 °C also led to formation of IPs but in low yield (77SUP557758, 82USP4336257).

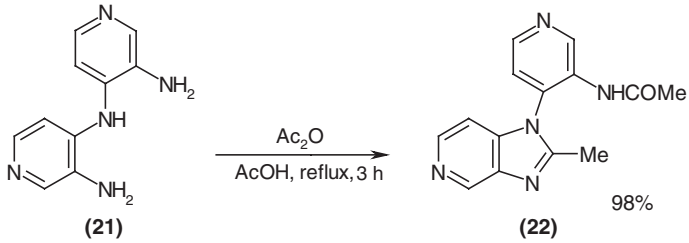
2,3-DAP was readily cyclized with glycolic acid to give 2-hydroxymethyl-IbP, whereas thioglycolic acid boiled with the same diamine **18** in benzene or toluene in the presence of dimethyl carbonate or 2,6-dichlorobenzaldehyde furnished IP's derivatives **20** with unusual structure, but in relatively poor yields (94FES345).



(20)

	R^1	R^2	yield, %
a	OMe	OMe	38
b	H	2,6-$Cl_2C_6H_3$	26

However, formation of IP is known to occur also under rather mild conditions. For example, imidazopyridine **22** was obtained as a result of boiling a mixture of 2,3′-diamino-4,4′-dipyridylamine **21** with excess Ac_2O in the presence of acetic acid (96ZOR586).

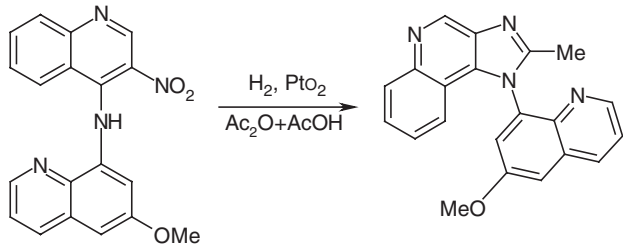


(21) **(22)**

The same method was used to obtain the corresponding IPs (71KG693, 74UKZ258) from N-substituted diamines.

Ring formation of 5-NH_2-2-Me-IP occurs while reducing 3-nitro-2,6-bisacetylaminopyridine (47JA1151) with tin(II) chloride in hydrochloric acid.

IP benzo derivative **24** is formed while reducing the nitro derivative of diquinolylamine **23** with hydrogen in a mixture of acetic acid and its anhydride (50JOC1278) under 60 pounds pressure in the presence of platinum catalyst.



(23) **(24)**

The regioselective synthesis of 3-substituted IbP may by accomplished by heating 2-formylamino-3-aminopyridine with benzyl or allylbromides in the presence of caesium carbonate (95JOC960).

The above work (48JCS1389) which reported the necessity of maintaining high temperature conditions for the successful cyclization of 5-bromo-2,3-diacylamines to IPs, also contained an account of IP formation from diamine and a small excess of formic acid (98%) after only 1 h of reflux. This result contradicts data reported in (64JOC3403, 52CB1012). But the stated method was repeated to obtain IcP 2 from 3,4-DAP and HCOOH (56JCS4683). Unfortunately, the authors failed to report the details about the reaction temperature. But if there is a small excess of formic acid, which has been converted to its salt with DAP, then the temperature of a mixture subjected to reflux might be high enough to give an imidazole ring. Mizuno et al. once again reproduced the procedure published in (48JCS1389). The results of this thoroughly performed experiment showed that IP arose immediately on refluxing a mixture of 2,3-DAP with a small excess of HCOOH. Sublimation *in vacuo* of the product did not change its melting point and other properties offering a proof of structure (63JOC1837).

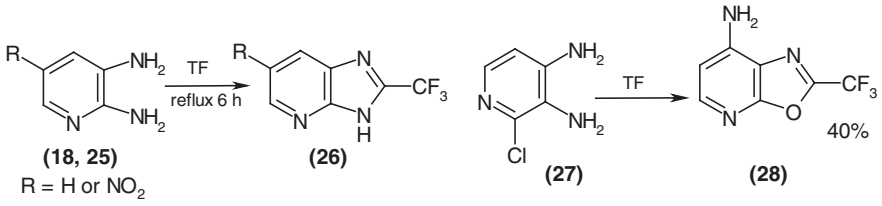
The descriptions of the conditions of DAPs cyclization with carboxylic acids and their derivatives were rather vague and contradictory. The authors (62JPR199) reported the impossibility of 3,4-DAP cyclization with carboxylic acids or their derivatives but obtained 2-methyl-IcP from the mentioned diamine and a large excess of acetic anhydride. Here, the mixture is boiled for 2–3 h, then distillation with Ac_2O takes place, and its aqueous solution is neutralized. However, this account contradicts data reported in (27CB766, 38CB2347, 64JOC3403).

Different reports contain different results dealing with *o*-DAP cyclization with formic acid (57JA670). However, the type of substituents affects the ease of IP formation. Thus, unsubstituted 3,4- and 2,3-DAP are very reluctant to undergo cyclization. The presence of a halogen atom in the diamines facilitates their cyclization into IPs to such an extent that in some cases it is enough to reflux the parent substances or to evaporate the reaction mixture (27CB766, 49JA1885, 57MI1, 59JOC1455, 60CPB539, 65JHC196, 72RTC650).

Halogen atoms at active positions in the pyridine ring do not necessarily undergo solvolysis even when 4,6-dichloro-2,3-diaminoPy is heated with HCOOH for many hours (72RTC650). But this is not always true. Such chloro-substituted 2-Cl-3,4-diNH_2Py, when refluxed with 98% HCOOH is converted into 4-hydroxy IP derivatives (64RZC887, 67RZC1887).

Heating the 2-Cl-3,4-diNH_2Py with valeric acid anhydride in refluxing THF gives 4-hydroxy-IcP (94JMC1632). Nitro-, amino- and hydroxy-substituted *o*-DAPs seem to be more readily converted into IPs than the unsubstituted diamines (49JA1885, 56JA4130, 57JA6421, 65SWP386442, 66CB254, 68IJC123, 69JHC759).

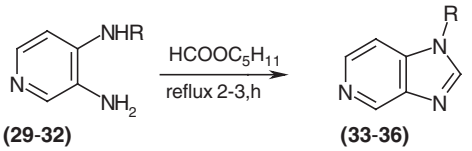
N-substituted *o*-DAPs are cyclized with formic acid and Ac_2O to afford IP more readily than unsubstituted diamines (60CPB539, 68IJC123). Undoubtedly the strength of the carboxylic acid affects the IP formation rate, but no special studies have been carried out. As seen above, *o*-DAP more readily underwent cyclization with formic acid than with acetic acid and even more easily with trifluoroacetic acid and its anhydride (71CB344) (**18, 25** → **26**). It should be noted that with 2-chloro-3,4-DAP **27**, abnormal cyclization resulting in formation of oxazolopyridine **28** occurred (71CB344).



Since *N*-acylation of *o*-DAP is known to precede the imidazole ring conversion into IP, it would be useful to measure the extent of such conversions by carbonyl band disappearance in the IR spectrum of the product.

In some cases, carboxylic acid esters were used for *o*-DAP cyclization, including *o*-esters. When a mixture of 2,3,4-triaminopyridines and a large excess of triethyl orthoformate in concentrated HCl is stored at room temperature for a long time, it affords a mixture of IbPs and IcPs in 97% overall yield (87JMC1746).

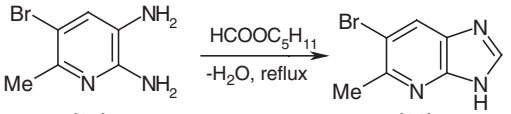
Amyl formate is an effective cyclizing agent for *o*-DAPs (for example, **29**, **30**, **31**, and **32**) providing IPs **33**, **34**, **35**, and **36** in high yields (80SUP717055). In this case the high boiling temperature of amyl formate favoured the reaction.



(29-32) (33-36)

	R	yield, %
29, 35	Me	95
31, 33	CH_2Ph	95
30, 36	Ph	87
32, 34	c-C_6H_{11}	80

It was recommended to carry out this type of cyclization (for example, **37** to **38**) by distilling out azeotropic water and amyl formate (97SUP1262927).



(37) **(38)**

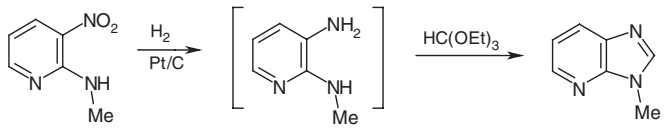
Ethyl diethoxyacetate reacted with 2,3- and 3,4-DAP in the presence of sodium methylate at 120–140 °C to afford IPs 2-aldehyde acetals (yields 26 and 24%) (71AJC2389).

Ethyl orthoacetate (76USP3996233, 77USP4003908) and ethyl orthoformate in large excess (76USP3996233, 77USP4003908, 77USP4043182, 78USP4088654, 81USP4276293, 94JMC305, 95JOC960) were used to cyclize *o*-DAP, sometimes in the presence of catalytic quantities of HCl or *p*-toluenesulphonic acid. This procedure was used to prepare IPs from tetra- and triaminoPy (73JMC292, 73JOC613).

Imidazo[4,5-b]pyridine-6-sulphamide (57MI1, 57JA6421) was obtained by boiling 2,3-diamine-5-sulphamide hydrochloride in ethyl orthoformate.

Israel et al. (69JHC759) not only heated 2,3-diamine-5-methylpyridine with ethyl orthoformate, but also subjected the mixture to a vacuum distillation to obtain 5-methyl IbP in 77% yield.

In the patent (67SUP201410), a reduction of 3-nitro-2-methylaminopyridine **39** with hydrogen under atmospheric pressure at room temperature in ethyl orthoformate with further cyclization of the forming *o*-DAP **40** to IP **41** was described. But when DAP **40** is obtained from nitroaminopyridine **39** by hydrogenation followed by isolation and purification of the product in air, the product is easily oxidized. The latter procedure provides a possibility to avoid oxidation, and as a result the yield of the target IPs **41** reached 80% with respect to the parent nitrocompound **39**.

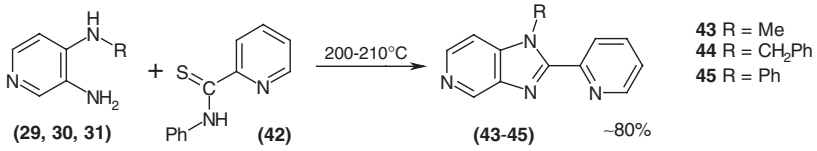


(39) **(40)** **(41)**

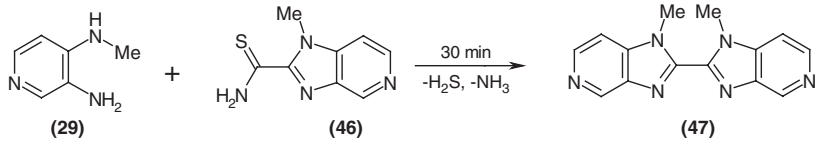
Cyclization of *o*-DAP readily occurred either in a mixture of ethyl orthoformate or ethyl orthoacetate and acetic anhydride giving either IP unsubstituted in the position 2 or its 2-methyl derivative in 86 and 93% yield (73UKZ274). The same mixture can be used to convert 5-NO_2-3,4-diaminoPy into 7-nitro-IcP (73UKZ350). This method was also used to prevent the solvolysis of a chloro group during the preparation of 4-chloro-IcP from 2-chloro-3,4-DAP (66JCS(B)285, 73UKZ703), in contrast to the reaction of the same diamine with anhydrous formic acid (64RZC887, 67RZC1887). The mixture of orthoformic ester with acetic anhydride is in equilibrium with diethoxymethyl acetate (37JOC260), and the latter is an effective cyclizing agent (74RTC3, 90JHC563).

Formamide and 2,3-DAP-5-sulphonic acid afforded IbP-6-sulphonic acid (62%) (57MI1, 57JA6421).

Substituted 2,3-DAP heated at reflux with a mixture of DMF and DMA furnished 3-(3- dimethylaminoethylindolyl-5)-IP in 63% yield (95MI8). The fusion of an equimolar mixture of pyridine thioamide and 2,3- or 3,4-DAP at 290 °C provided 2-(pyridinyl-2)-IPs (yields not mentioned) (78MI4). Successful results were obtained when stoichiometric amounts of DAP **29**, **30** and **31** and picolinic acid thioanilide **32** were heated at 155–210 °C (89KG940). The formation of 2-(pyridyl-2)-IPs **43**–**45** was accompanied by hydrogen sulphide and aniline liberation.



In the same publication, the preparation in 75% yield of symmetrical bis(1-methyl-IcP-2-yl) **47** by heating equimolar amounts of DAP **29** and thioamides **46** at 170–190 °C was also described.



2,5-Dimethoxybenzoic acid thiomorpholide methiodide easily reacted with 3,4-DAP at 120 °C (2 h) giving rise to 2-(2,5-dimethoxyphenyl)-IP (83BRP2113675).

Iminoesters were used to synthesize IP 2-benzyl derivatives from 2,3-DAP; however, the products were obtained in yields not exceeding 50% (92FES287).

Amidines have not found wide application for *o*-DAP cyclization apparently because they have no special advantages over other more accessible reagents. Mizuno et al. described the cyclization of *o*-DAP with formamidine acetate providing poor yields of IPs. In one case the parent substances were refluxed in 2-methoxyethanol, and in the other instance the heating at reflux of the parent substances was followed by vacuum distillation (63JOC1837). Reaction of *o*-DAP and potassium dithioformate (48RTC29, 69RTC1263) afforded relatively poor yields of IP. The synthesis of

2-(benzimidazolyl-2)-IbP from 2,3-DAP **18** and 2-trichloromethylbenzimidazole in 40% yield (67JCS(C)33) may be of interest.

The problem of getting reliable results for the cyclization of *o*-DAP into IPs was solved by carrying out the reaction in a strong dehydrating medium: PPA, $POCl_3$, $SOCl_2$, $COCl_2$, *p*-toluene sulphonic acid (TSA), etc. The most common procedures apply PPA. Garmaise and Komlossy reported that an equimolar mixture of 2,3-DAP and aromatic heterocyclic acids with a large excess of PPA gave 2-phenyl and hetaryl IPs in 41–90% yield (64JOC3403) when heated at 175 °C, whereas heating the same diamine with benzoic anhydride at 180 °C resulted only in the formation of 2,3-dibenzoyldiaminopyridine.

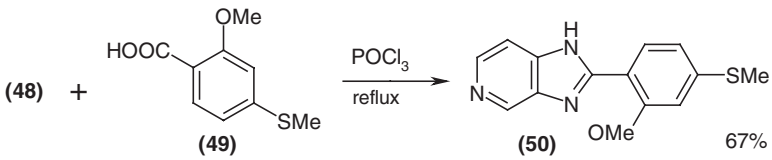
Various 2-alkyl (79IJC428, 81MI1, 91JMC2919), 2-aryl (including aminophenyl) (80OPP234, 80JHC1757, 83BRP2113675, 89JHC289, 90JHC1825), 2-pyridyl (90JHC1777) derivatives of IbP and IcP were obtained under similar conditions. The yields of 2-alkyl(cycloalkyl)-IP attained 44–95%, those of 2-phenyl-IPs were 86–95%. In other studies the cyclization of *o*-DAP in the PPA medium was carried out at 80–100 °C (78IJC531, 84GEP3225386, 94MI1, 94JCR(S)426). When heated in PPA (160–170 °C, 1 h), *N*-acetyl derivatives of 2-chloro-3,4-DAP transformed into 4-chloro-2-methyl-IcP in 46% yield (73UKZ703). The cyclization of 3,4-DAP with isoquinoline-1- and -3-carbonitriles (67JHC483), as well as with picolinic acid nitriles and its derivatives (67JHC157) was performed in PPA. However, nitriles as compared with carboxylic acids require high temperature (250 °C) and give poor yields of IPs (18–47%) and so do not show any advantage.

Under milder conditions (180 °C, 2 h) 2-chloromethyl-IPs were obtained from 2,3-DAP, 3,4-DAP and chloroacetonitrile (yields 35, 8 and 70%) (71LA158).

Instead of PPA, Robertson et al. used a mixture of phosphoric acid anhydride and methanesulphonic acid at 100–120 °C, but the yield of 2-*p*-toluyl-IcP from 3,4-DAP and toluic acid was less than 22% (85JMC717).

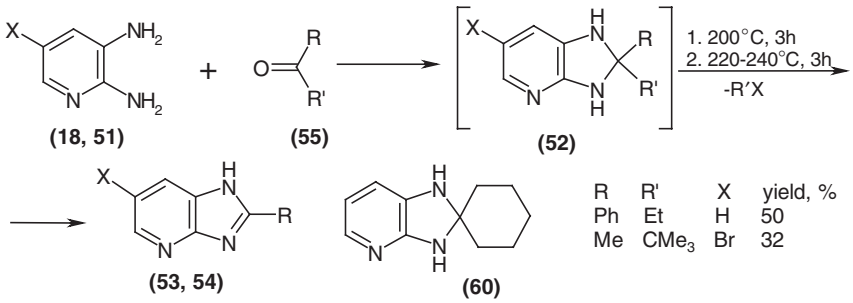
PPA is a reliable agent for *o*-DAP cyclization to IPs. But its application often caused great problems for the isolation of product out of a large amount of water–salt solutions formed after dilution of the mixture with water and phosphoric acid neutralization.

Instead of PPA, it is better to use phosphorus oxychloride or thionyl chloride that can be distilled from the mixture on completion. As a rule these reagents give the same yields as PPA. For example, refluxing a mixture of 2,3-DAP and 2,4-dimethoxybenzoic acid in $POCl_3$ afforded 2-(2,4-dimethoxyphenyl)-IcP in 85% yield (77SUP563917). In the case of other alkoxybenzoic acids, lower yields of IPs were obtained (90AP501). Using the same procedure IP **50** (precursor of isomazole) (85MI6) and other 2-phenyl-IPs (83BRP2113675, 85JMC717) were prepared from 3,4-DAP **48** and acid **49**.



An alternative method using a pyridine medium with a three-fold excess of $POCl_3$ furnished compound **50** in 67% yield (85MI6). In place of pyridine, DMF can be used. For example, keeping for 2 h a mixture of 4-chloro-2,3-DAP in a large molar excess of DMF with a small excess of $POCl_3$ near room temperature afforded 6-chloro-IbP in 96% yield (69RTC1263). 4-Chloro-IcP and 4,7-dichloro-IbP were prepared analogously in high yields. 3,4-DAP reacted with substituted benzoic acid morpholide in $POCl_3$ under reflux to give 2-phenyl-IcP (83BRP2113675).

The cyclization of *o*-DAP in the presence of $POCl_3$, $SOCl_2$ or TSA was described for carboxylic acids, nitriles, and amides, as well as for thioamides, dithioacids, orthoesters, anhydrides, acyl chlorides, and esters (77SUP563917). Along with carboxylic acids and their derivatives aldehydes and ketones are used for IP synthesis. The reaction between diamines **18** and **51** and ketones **(55)** first provides dihydro-IPs **52** that eliminate a hydrocarbon when heated to high temperature furnishing aromatic IP **53** and **54**. Apparently dihydroimidazoles **52** readily formed under mild conditions because heating diamine **18** with cyclohexanone in methanol gave 2,2-spirocyclohexano-2,3-dihydro-1H-IbP **60** (80IJC863).



The first syntheses of IcP, also including unsubstituted **2**, **86**, **61** and **62** were carried out with 3,4-DAPs **29** and **48** and aliphatic or aromatic aldehydes. A specific feature of a procedure described by Weidenhagen et al. was the application of an oxidant, copper(II) acetate (38CB2347), to complete imidazole ring formation. This reaction was later extended to the synthesis of other IPs derivatives (42CB1936).

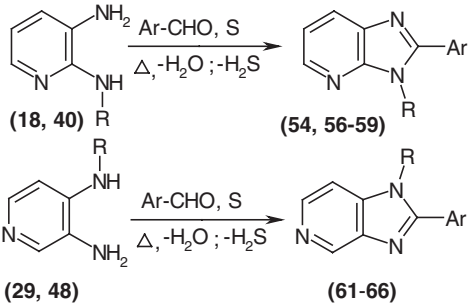
This cyclization usually takes place under mild conditions, and IP's yields are within 44–71%. The product is an IP copper salt that is decomposed by hydrogen sulphide. The preparative value of this important method of IP's synthesis is diminished by the necessity of treating the salt with hydrogen sulphide due to difficulties in the IP isolation. Moreover, Knobloch and Kuhne pointed out that in some cases Weidenhagen's method failed (62JPR199). It is also possible to use other oxidants instead of copper(II) salt. For example, diamine 5-Cl-3-NH_2-*p*-$ClC_6H_4CH_2Py$ with the monoester of 3,3-dimethylglutaricaldehyde gave dihydro-IP, which then was oxidized by iodine at 50 °C in dimethoxyethane affording IP 3-*p*-Cl-benzyl-6-Cl-IbP-2-dimethylbutanoic acid (94JHC73).

As shown by Dubey and Ratnam, the reaction of 2,3-DAP with an aldehyde occurred at the amino group in position 3 giving an azomethine that then was

converted into dihydroimidazole, the latter being oxidized either by oxygen in air or by a large excess of nitrobenzene to give IP in 30–65% yields (77PIA(A)204).

Diamine **18** with cinnamaldehyde upon heating in nitrobenzene furnished 2styryl-IP (79IJC428), whereas 5-bromo-2,3-DAP upon heating in nitrobenzene with benzaldehyde gave 5-bromo-2-phenyl-IcP in 80% yield (80IJC863).

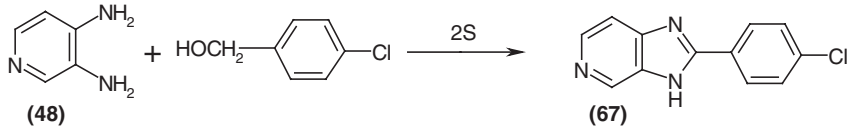
The preparative application of nitrobenzene as oxidant is inconvenient, and a better agent is elemental sulphur. Taken in an equimolar amount to diamine **18**, **29**, **40** and **48** and aldehyde sulphur smoothly oxidized the intermediate IP dihydro derivatives to 2-aryl-IPs (**54**, **56**, **57**, **61**, **62**, and **58**–**66**) with yields within 76–93%. The reaction occurred on fusion of the three components at 165–175 °C or on heating them in xylene until the end of hydrogen sulphide evolution. In both cases, only the target product, i.e. 2-aryl-IP, remained in the mixture with xylene solvent when the reaction was carried out by the second procedure (77SUP566842, 87KG639).



	R	Ar	yield, %
54	H	Ph	93
56	H	4-ClPh	84
57	H	thyenyl-2	75
58	H	4-MeOPh	87
59	Me	1-Me-indolyl-2	75
61	H	Ph	91
62	Me	Ph	82
63	H	4-Me_2NPh	88
64	Me	2-(HO)-3(MeO)Ph	92
65	Me	4-(HO)-3(MeO)	93
66	Me	z2,5-(MeO_2)Ph	85

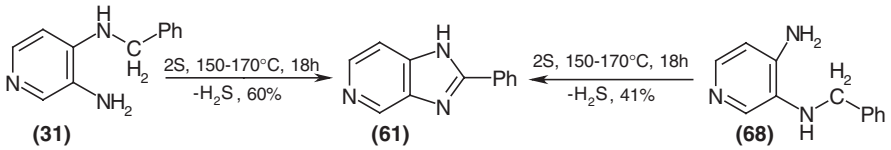
More recent patents give an account of *o*-DAP reactions with aromatic aldehydes and sulphur affording 2-aryl-IPs. A reference to the initial patent containing the description of the above procedure for IP preparation (77SUP566842) was given in (83BRP2113675). Unfortunately this information is absent in (83GEP3132754).

Benzyl alcohols as aldehyde precursors were also added to similar reactions utilizing the oxidizing properties of sulphur (87KG639). Diamine **109** and benzyl alcohol were heated with sulphur at 180–200 °C to obtain 2-phenyl-IP **54** in a poor yield (20%). A similar reaction occurred easier with *p*-chlorobenzyl alcohol; here the yield of 2-*p*-chlorophenyl-IcP **67** reached 60% (87KG639).

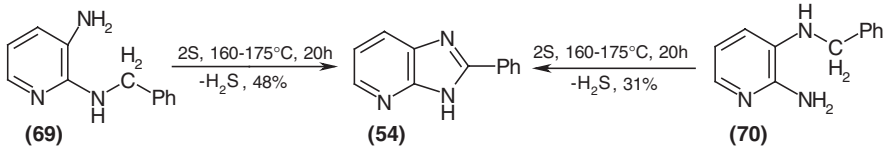


If instead of benzyl alcohols the corresponding quaternary salts were used, namely 1-benzyl and 1-(4-chlorobenzyl)pyridinium chlorides, the reaction with diamine and sulphur resulted in poor yields of IPs (35%). Unlike the above compounds, *N*, *N*-dimethylbenzylamine did not react with *o*-DAP and sulphur. However, the reaction can take place intramolecularly when the N-benzyl group is a structural fragment of the diamine molecule. When both 3-amino-4-benzylaminopyridine **31**

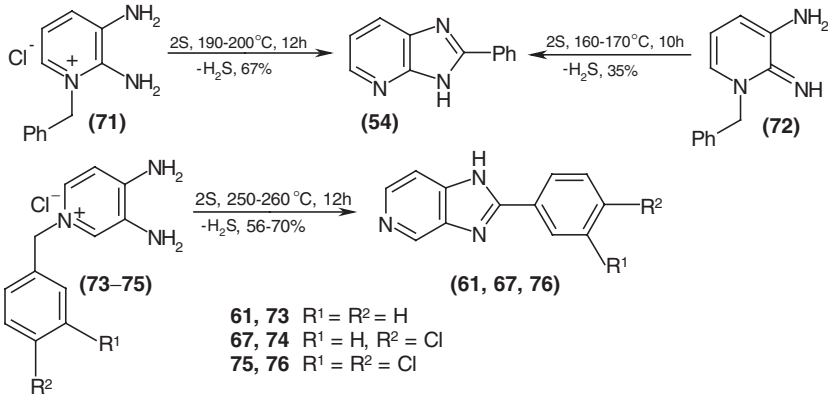
and 4-amino-3-benzylaminopyridine **68** were heated with sulphur the same 2-phenyl-IcP **61** was formed in satisfactory yield (87KG639).



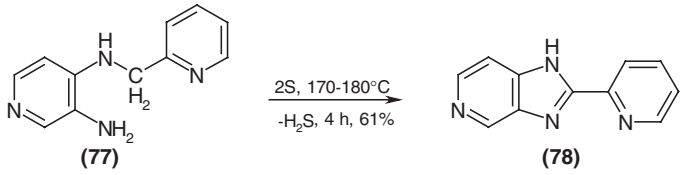
IbP **54** was prepared from diamines **69** and **70** under similar conditions.



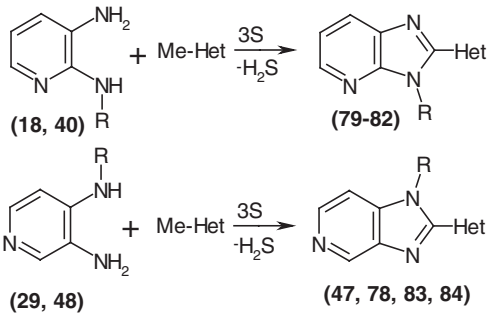
The oxidative cyclization of diamines also occurred when a benzyl group was attached to the nitrogen of the pyridine ring. The oxidation and loss of the benzyl group with further cyclization to IP **54**, **61**, **67**, and **76** took place at fusion of sulphur with chlorides **71** and **73–75** or bases **72** (87KG639) obtained from these chlorides.



Analogously to the conversion of N-benzyl-substituted *o*-DAPs **31** and **68**, **69**, **70**, **71**, and **72** into 2-phenyl-IP **54** and **61**, the intramolecular cyclization of 3-amino-4-(pyridyl-2-methylamino)pyridine **77** on fusion with sulphur led to the formation of 2-(pyridyl-2)-IP **78** (89KG940).

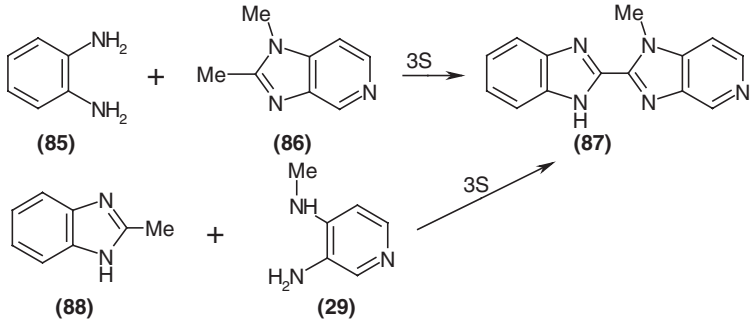


This reaction is facilitated by the proximity of the amino groups to the methylene group and also by activation of the latter in the α-position of the pyridine ring. Similarly, but in an intermolecular mode, *o*-DAP reacted with compounds of the α- and γ-picoline type. The reaction readily occurred on fusion with equivalent amounts of sulphur, *o*-DAP **18**, **29**, **40**, and **48** and an aromatic N-heterocycle containing an active methyl group for 3–15 h at 140–200 °C furnishing various 2-hetaryl-IPs (**47**, **78**, and **79**–**84**) in 70–98% yields (77KG553, 77SUP545646, 89KG940) with H_2S evolution.



	R	Het	yield, %
47	Me	1-MeIcP-2-yl	98
78	H	Py-2	85
79	H	6-Me-Py-2	87
80	H	IcP-2-yl	98
81	H	quinolyl-2	90
82	Me	quinolyl-2	80
83	H	quinolyl-2	82
84	Me	Benzothiazolyl-2	84

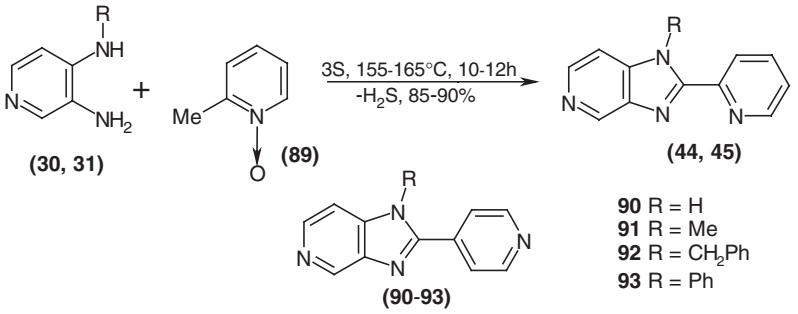
Due to its relative simplicity, this reaction is frequently applied to the synthesis of fused 2,2-bisimidazoles, as for example **87**, from various pairs of diamines and methylheterocycles (**86** + **85** and **29** + **88**).



The mechanism is likely to include the formation of an intermediate thioamide belonging to Wilgerodt–Kindler's type, then cyclized into the final 2-hetaryl-IP with simultaneous hydrogen sulphide liberation. These intermediate thioamides were not isolated. However, as mentioned, the fusion of *o*-DAP **29** with picoline-2-thiocarboxylic acid anilide (**42**) easily afforded 2-pyridyl-IP (**43**) in a high yield, giving also aniline as a by-product (89KG940).

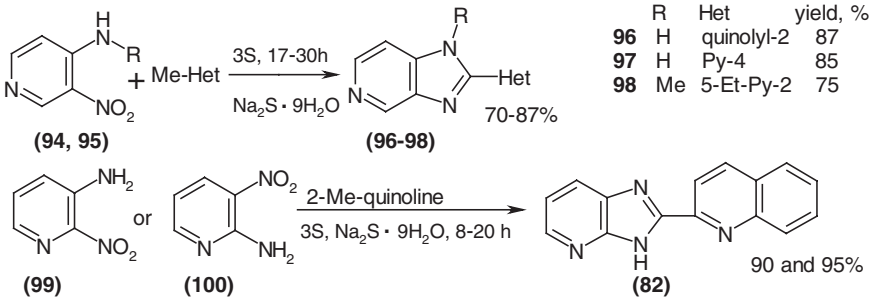
One possible modification of the oxidative cyclization of *o*-DAP can be performed by replacement of the α-methylheterocycles with their N-oxides. The fusion of a

mixture of *o*-DAP **30** and **31**, α-picoline **89** and γ-picoline N-oxides with sulphur at 150–160 °C resulted in the formation of 2-pyridyl-IP derivatives (**44**, **45**, and **90**–**93**), but no corresponding N-oxides were obtained, because the hydrogen sulphide liberated in the reaction apparently reduced the N→O group.



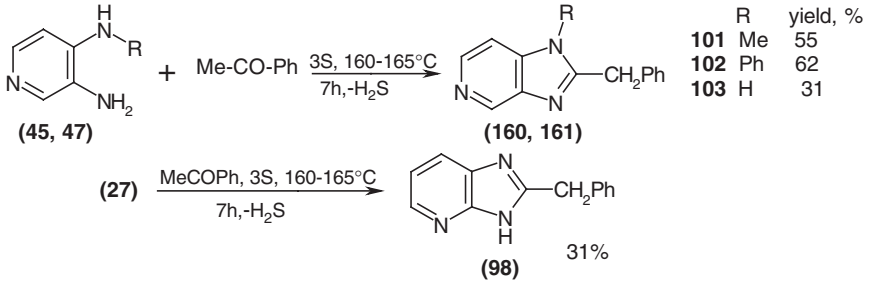
This type of synthesis of 2-hetaryl-IPs is simpler, affording products in 60–90% yield, while according to (67JHC157, 82USP4336257) the yields were 11–20%, or no more than 30%. The structures of the 2-hetaryl-IPs along with chemical proofs were also confirmed by mass and PMR data (89KG940).

Another useful modification is the use of available *o*-DAP's precursors like *o*-nitroaminopyridines instead of *o*-DAP itself, because the former can be reduced to diamines by hydrogen sulphide evolved during the reaction. Fusion of *o*-nitroaminopyridines **94**, **95**, **99**, and **100** with methylheterocycles and sulphur (160–180 °C) afforded 2-hetaryl-IPs but in a poor yield (5–23%). However, using a mixture of sulphur with sodium sulphide in 3:1 ratio resulted in higher yields (up to 70–95%) of IPs **82** and **96**–**98** while the reaction temperature was reduced to 140–155 °C (94ZOR429).



IP's yields do not depend on the location (2,3- or 3,2-) of the amino and nitro groups in the parent *o*-nitroamines. This method can be used as well to obtain 2-hetarylbenzimidazoles in high yields (85–96%) from *o*-nitroanilines (94ZOR429).

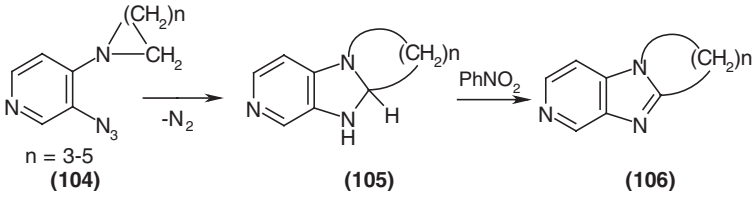
Acetophenone can be regarded as an analogue of heterocycles with a reactive methyl group. 2-Benzyl-IP's **101**, **103** and **102** (94ZOR460) were obtained by heating acetophenone with *o*-DAP **18**, **29** and **30** and sulphur.



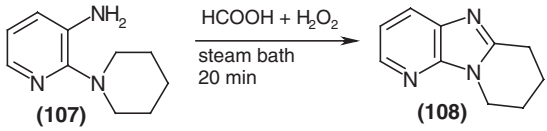
The fact that acetophenone reacted with *o*-DAP at its methyl group and not its carbonyl group which was reduced to a methylene group suggested that the first stages of the process proceeded as a Wilgerodt-type reaction. Based on this observation it is expected that IP can be formed from other substances capable of reacting according to the Wilgerodt reaction. For example, heating *o*-DAP with styrene as well as with phenylacetylene afforded the same IPs as from acetophenone but in higher yields (95UP).

More examples can be provided to illustrate IP formation by reactions that take place in the presence of oxidizing agents.

Heating 2- and 4-dialkylamino-3-azidopyridines **104** in nitrobenzene at 170 °C results in a loss of nitrogen from the azide group to give a nitrene that attacks the α-methylene group of the *o*-dialkylamino substituent with further formation of dihydroimidazoles **105**, which are then oxidized by nitrobenzene to IPs **106**. Here IcP yields are 40–70%, and the yields of IbPs do not exceed 10–15% (63JCS1666).



A mixture of hydrogen peroxide and formic acid oxidized *o*-DAP **107** containing a tertiary nitrogen atom to give IP **108** in 15–20% yield (66JCS(C)80).



Along with the above oxidative reactions, there are other cases of IP formation under the action of reducing agents.

Such an example is the formation of 7-NH_2-5-EtOOCNH-2-phenyl-IbP (yield 22.5%) from an equimolar mixture of 3-NO_2-2,4-diNH_2-6-EtOOCNHPy

and benzaldehyde, when hydrogenated in alcohol in the presence of Raney nickel at atmospheric pressure and room temperature (87JMC1746).

The authors did not discuss the mechanism. Perhaps the intermediate diamine (tetramine) formed from the nitro compound reacts with benzaldehyde to give an azomethine and then a dihydroimidazole. The latter may be oxidized to IP by the nitro compound not yet reduced; the low yield of the reaction product supports this assumption.

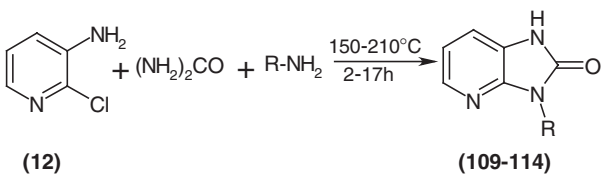
Stirring a mixture of 2-formylamino-3-nitropyridine, benzaldehyde and borane–pyridine complex in methylene chloride and acetic acid at room temperature afforded 1-benzyl-IbP. Similar derivatives of IbP were prepared from other aldehydes. The reaction of 3-benzylidenamino-2-formylaminopyridine with borane–pyridine complex also led to the formation of benzyl-IbP (95JOC960).

Under reflux of 2,3-DAP **18** with 2-phenyl-arylideneoxazolone 2-PhCONH-(ArCH =)C-IPs formed in a good yield. The fusion of the same components with sodium acetate yielded the aminopyridyl derivative of arylidenoimidazolone, which on boiling in the mixture of acetic acid and sodium acetate was converted into the complex IP, imidazo(5′,1′:2,3)imidazo(4,5-b)pyridine (89CCC1096).

2. *2-Oxo-, 2-Thio- and 2-Aminoimidazopyridines*

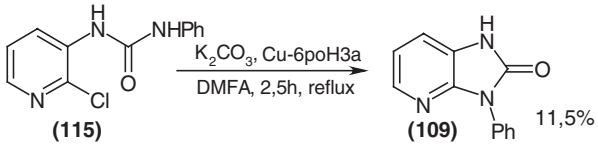
IPs with substituents like oxo(hydroxy)- or thio(thioxy)- in position 2 are the most available compounds. They are usually obtained from *o*-DAPs, but 2-oxo-IPs can be produced from certain *ortho*-substituted monoaminopyridines.

2-Chloro-3-aminopyridine **12** (36CB2593) fused with aniline and urea was converted into 3-phenyl-3H-IbP-2-one **109** in 99% yield. Other anilines, as well as benzylamine gave rise to imidazolones **110**–**114** in relatively poor yields (97SUP921235).



	R	yield
109	Ph	99
110	m-FPh	55.5
111	m-MePh	55.5
112	m-MeOPh	48.5
113	2,4-$(MeO)_2$Ph	33
114	$PhCH_2$	35

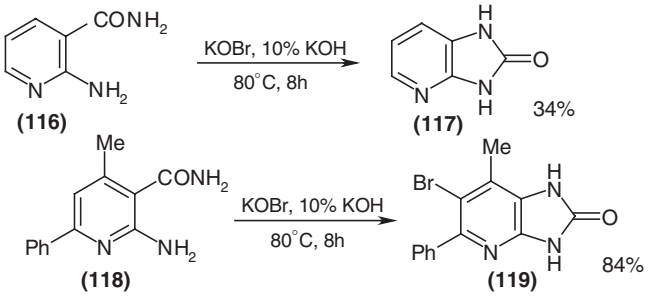
On heating 2-chloro-3-aminopyridine **12** with phenyl isocyanate in toluene phenylpyridylurea **115** was obtained, which was capable of intramolecular cyclization resulting in imidazolone **109,** although in a poor yield (76GEP2623469).



Derivatives of 2-aminonicotinic and 3-aminopicolinic acids are also suitable for the preparation of 2-oxo-IPs. Heating unsubstituted nicotinamide **116** with an

alkaline solution of potassium hypobromite led to the formation of IbP-2-one **117**, whereas amides with methyl and phenyl substituents at the pyridine ring furnished a brominated IbP-2-one (**118** → **119**).

However, the cyclization of pyridine with hypobromite in methanol was not accompanied by bromination of IP-2-ones. In contrast, the reaction of 6-oxy-2-amino-nicotinamide with sodium hypochlorite provided 6-chloro-IP-2,4-dione (57AP20).

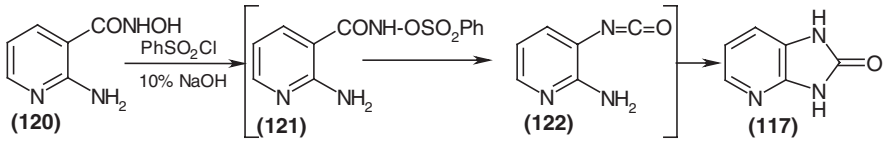


Imidazolone of a more complex structure was obtained by bromination of 2-(3-oxypropyl)amino-5-(oxopyridyl-4)nicotinic amide in the presence of alkali in 53% yield (94MI5).

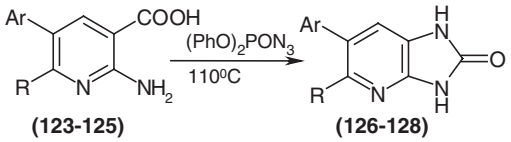
Heating of 3-amino-2-picolinic acid azide in toluene for a short duration gave IP-2-one in 50% yield, whereas the thermolysis of 2-aminonicotinoyl azide in xylene led to the formation of the same imidazolone but in 90% yield. This imidazolone is also formed in a relatively poor yield (~38%) on pyrolysis (210–220 °C) of both 3-aminopicolinoyl hydroxamic acid and its isomer, 2-aminonicotinoyl hydroxamic acid. In the latter case 2-aminonicotinic acid (59JCS3157) is formed as a by-product in 19% yield.

Heating 2-amino-5,6,7,8-tetrahydroquinoline-3-carboxylic acid azide in xylene starting from 90 °C and up to the boiling point gave 5,6-tetramethylene-IP-2-one in almost quantitative yield (58CB1834).

Sulphonation of hydroxamic acid **120** by a stoichiometric quantity of benzene-sulphonyl chloride in alkaline solution at 25 °C gave imidazolone **117** in 71% yield, but only after recrystallization of intermediate compounds **121** and **122** from alcohol (68JOC2543).



Another striking example of the synthesis of substituted IP-ones **126**–**128** consisted of heating 2-aminonicotinic acid derivatives **123**–**125** with diphenylphosphoryl azide in dioxane (93JHC37, 94JMC248).



(123-125) (126-128)

	Ar	R	yield, %
123, 126	4-Pyridinyl	CF_3	81
124, 127	4-Quinolinyl	CF_3	80
125, 128	Pyridinyl	Me	85

Conversions of compounds **116**, **120** and **123** into IP-2-ones described above belong to Hofmann-, Curtius- and Lossen-type reactions. Therefore the parent amides, hydroxamic acids and *o*-aminopyridinecarboxylic acid azides, may formally be regarded as derivatives of monoaminopyridines. The above compounds rearrange into *o*-diamines with various degrees of ease, while benzenesulphonate **121** is transformed into intermediate isocyanate **122** under extremely mild conditions (68JOC2543).

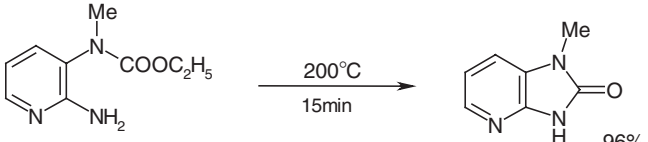
The reaction of *o*-DAP with urea remains the main procedure for the preparation of IP-2-ones. This reaction occurs on fusion of ureas with *o*-DAP at temperatures exceeding 100 °C (48JCS1389, 59JOC1455, 61USP3004978, 65JMC296, 66JCS(B)285, 69RZC573, 76KG1277, 76GEP2623469, 79USP4144341, 80JHC1757, 94H529). The cyclization is carried out with diamine or its hydrochloride also giving ammonia or ammonium chloride, respectively.

In some cases the cyclization of diamine with urea is carried out in solution, for example, in DMF (81USP4294837, 82USP4309537).

1,1-Carbonyldiimidazole (CDI) is known to be an excellent cyclizing reagent for *o*-DAP. The reaction of diamine with this reagent takes place at relatively moderate temperature in solvents (e.g., chloroform, DMF, etc.) (80USP4195088, 81SUP795478, 81USP4294836, 81USP4294837, 82USP4309537, 82USP4317909) or upon fusion (79BRP2006758, 81SUP795478, 81USP4247556) providing fairly good yields of IP. Imidazole is a by-product.

Besides urea and CDI, phosgene can be used for the cyclization of *o*-DAP (49JA1885, 78JMC965, 79USP4144341, 80JHC1757). Reaction takes place when phosgene is passed through the solution of diamine in diluted hydrochloric acid. This method is seldom used due to the high toxicity of the reagent and poor yields of IP-2-ones.

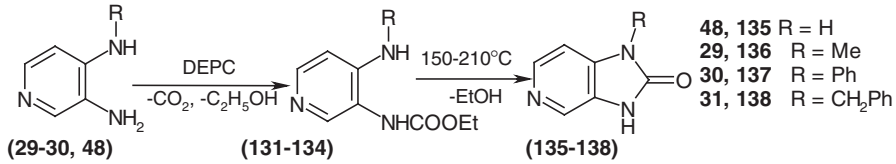
The thermal cyclization of *o*-DAP *N*-ethoxycarbonyl derivatives is extensively used. These derivatives are obtained by treating the diamine with chloroformate or by a Curtius reaction. Heating these ethoxycarbonyldiamines at 160–220 °C for 5 min to 3 h affords imidazolones (e.g., **129** → **130**), often in high yields (57JCS442, 76USP3996233, 77SUP557758, 79CZ387, 81SUP795478, 81USP4247556).



(129) (130)

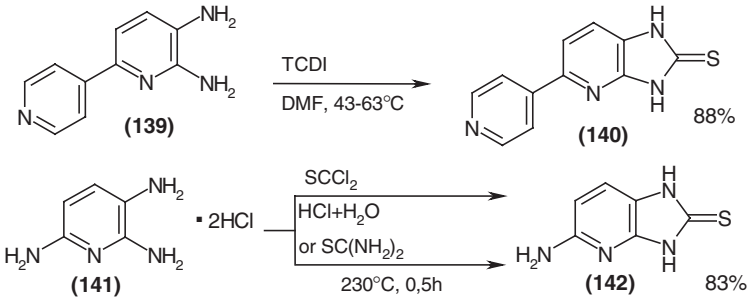
Diethyl pyrocarbonate (DEPC) is a more convenient reagent for IP-2-ones synthesis. DEPC reacts with *o*-DAP **29**, **30**, **31** and **48** on cooling with ice to give diamine *N*-ethoxycarbonyl derivatives **131**–**134** with liberation of carbon dioxide. On

heating the product to 150–210 °C for 0.25–1 h, alcohol is eliminated and practically pure IP-2-ones **135**–**138** in 80–99% yields are formed (72SUP351851, 76KG1277). This method was used to prepare 15 compounds in the IbP and IcP series.

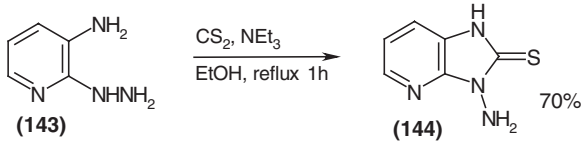


The DEPC reaction can also be used to prepare benzimidazolones. DEPC proved to be a better reagent for the preparation of water-soluble IP-2-ones than urea, phosgene or CDI.

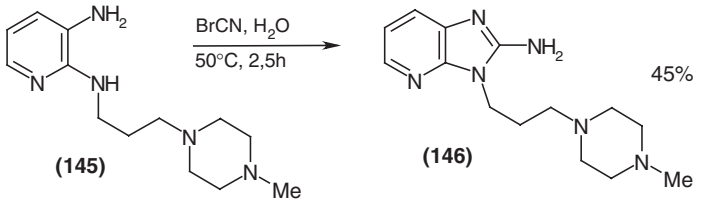
Imidazopyridine-2-thiones can be obtained following procedures similar to those used in the preparation of IP-2-ones. They are known to be formed from *o*-DAP on treatment with 1,1-thiocarbonyldiimidazole (**139** → **140**) [TCDI] (81USP4294836, 82USP4317909), thiophosgene (49JA1885, 79USP4144341, 80JHC1757) or thiourea (**141** → **142**) (48JCS1389, 80JHC1757).



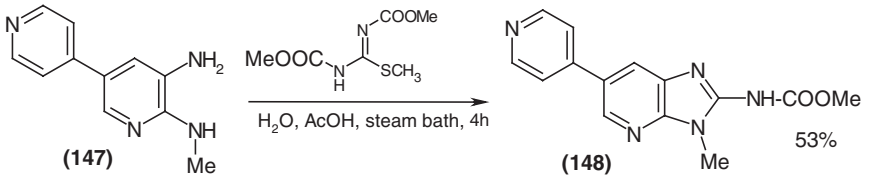
TCDI cyclizes *o*-diamines under mild conditions to give IP-2-thiones in high yields. However, carbon disulphide and potassium ethyl xanthogenate (PEX) are the most convenient and effective reagents for the synthesis of such thiones. Carbon disulphide was used either with a solvent (alcohol) (48JCS1389, 59JOC1455, 61USP3004978, 62JCS2379, 65JMC296) or in the presence of triethylamine (**143** → **144**) (77KG411), pyridine (66JCS(B)285, 88KG799) and alkali (48JCS1389, 79CZ387, 81USP4293696). Carbon disulphide on reacting with alkali is known to form alkali metal xanthogenates, and so this mixture is like pure potassium ethyl xanthogenate that also reacts with *o*-DAP to give thiones in high yields (79USP4144341, 81USP4294837, 88KG799).



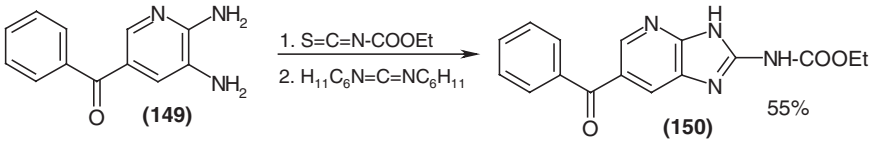
The well-known method of 2-aminobenzimidazoles preparation when *o*-phenylendiamines are treated by cyanogenbromide (60JCS2369) has proved to be successful for the synthesis of certain 2-amino-IPs from *o*-DAPs (77USP4059584, 81USP4247556, 94JHC1641). This reaction is carried out either in water or in alcohol at low (40–50 °C) or higher temperature (120 °C); unfortunately, yields of the target amines are poor (9%), a maximum 45% (**145** → **146**).



The reaction of *o*-DAP **147** with dimethyl 2-methylthiopseudourea-1,3-dicarboxylate gives 2-amino-IP **148** in satisfactory yield (83USP4391811).



When diamine **149** is successively treated with isothiocyanate and with dicyclohexylcarbodiimide, the latter being the acceptor of hydrogen sulphide on cyclization of the thiourea intermediate, IP **150** is obtained in satisfactory yield (90JHC1821).

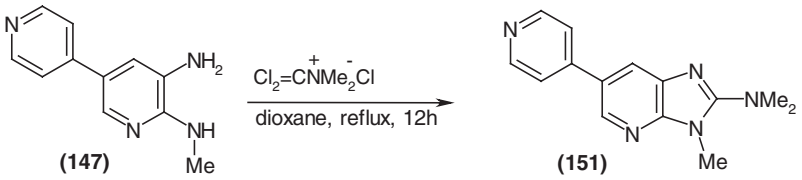


Mercuric oxide (80USP4219559) served as an acceptor of hydrogen sulphide while synthesizing 2-amino-IP from *o*-aminopyridyl thiourea.

An unusual synthesis of a derivative of 2-amino-IP by the reaction of 2,3-DAP **18** with 3[3-(1-piperidinyl-methyl)phenoxy]propylamine ketenimine thioacetal was claimed in a patent (84USP4447611). Components were heated in acetonitrile for 4 h followed by evaporation of the mixture with subsequent addition of DMF and

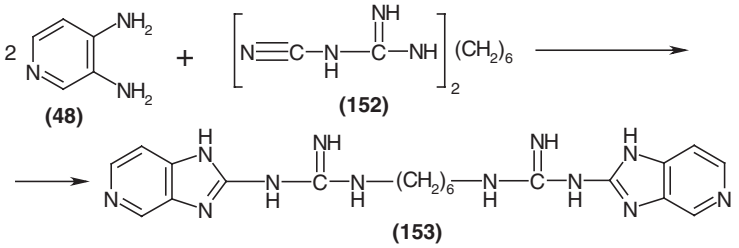
repeated heating of the resulting solution for 1 h at 120 °C. Unfortunately, this patent did not specify the yield of the target amine.

Heating at reflux of dichloromethylene-*N*,*N*-dimethylammonium chloride with diamine **147** in dioxane furnished 2-dimethylamino-IP **151** in good yield (83USP4391811).



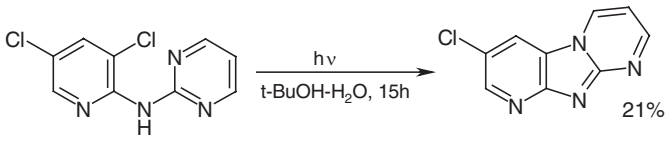
(147) (151)

Complex derivatives of cyanoguanidine such as di-(N^3-cyano-N^1-guanidino)hexane **152** react with 2,3- and 3,4-DAP giving bisimidazopyridylguanidylhexane **153** and similar compounds, whose yields are unreported (83USP4395552).



(48) (152) (153)

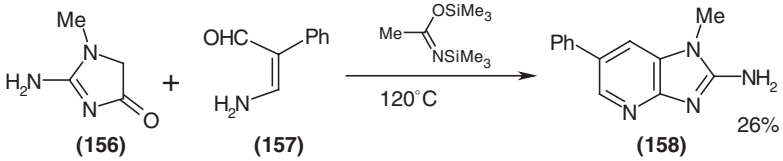
Unusual 2-amino-IP **155** derivative was claimed to be formed in poor yield when 2-(3,5-dichloropyridyl-2-amino)pyrimidine **154** was subjected to UV radiation (Hg lamp, 400 W) in aqueous *tert*-butanol (93ZOR2035).



(154) (155)

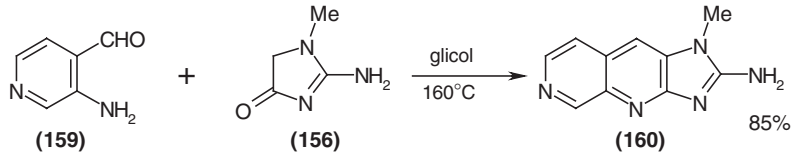
B. Syntheses from Imidazoles

The syntheses of IPs from imidazoles are less important due to the poor accessibility of the initial compounds. However, with simple imidazole derivatives these syntheses find limited application. Thus, 2-aminoimidazoline-4-one **156** was used to obtain IPs. Its interaction with β-amino-α-phenylacrolein **157** in the presence of the bistrimethylsilyl derivative of acetamide gave 2-amino-6-phenyl-1-methyl- IbP **158** in poor yield (95ACSA361).



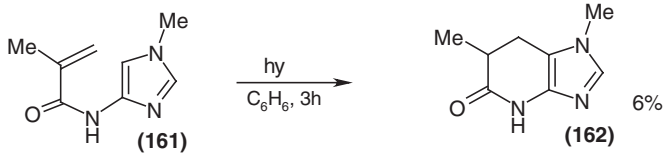
5,6-Benzo-IP (imidazo[4,5-b]quinoline) derivative formed in considerably higher yield (67%) when imidazolinone **156** was heated with *o*-aminobenzaldehyde in ethylene glycol (94SC1363).

The reaction of imidazolinone **156** with *o*-aminopyridine aldehydes **159** occurred in a similar way. Four isomeric imidazonaphthyridines (pyridoimidazopyridines) including **160** were thus synthesized (94JCR(S)268).

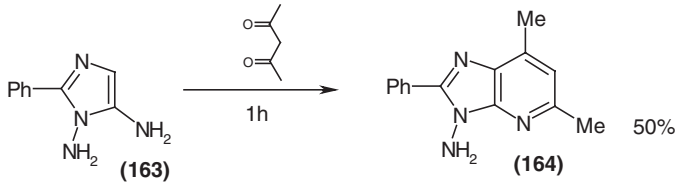


When heated in acetic anhydride, thiohydantoin reacted readily with *o*-aminobenzaldehyde affording IbP-2-thione 5,6-benzo derivative in 85% yield (31JIC241).

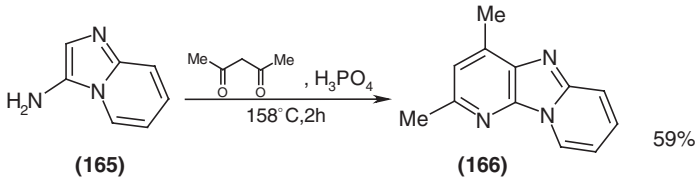
A classical example is the synthesis of 1,6-dimethyl-6,7-dihydro-IbP-5-one **162** when 4-methacrilaminoimidazole **161** is subjected to UV radiation (Hg lamp, 450 W) in benzene with the addition of ~0.6% acetic acid (72CPB2264).



1,5-Diamino-2-phenylimidazole **163** heated under reflux with excess acetylacetone gave IP **164** (83JHC1015).

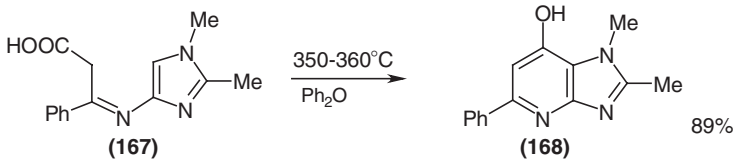


IP **166** with a somewhat unusual structure formed in good yield when 3-aminoimidazo[1,2-a]pyridine **165** was condensed with acetylacetone, the former playing the part of a 4-aminoimidazole derivative (94H1527).



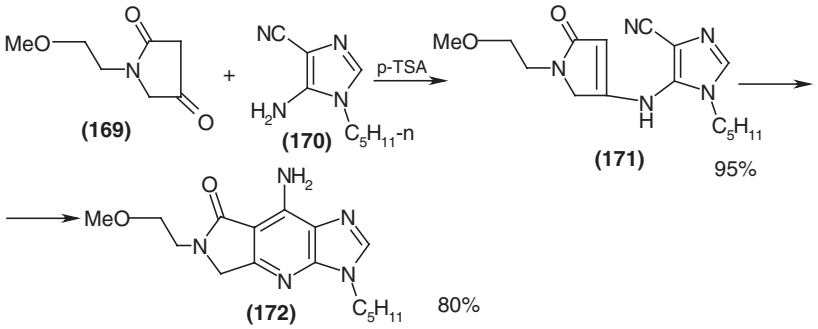
(165) (166)

Azomethine **167** obtained from 4-amino-1,2-dimethylimidazole was capable of intramolecular cyclization on heating in diphenyl oxide to afford IbP **168** (90JHC531).



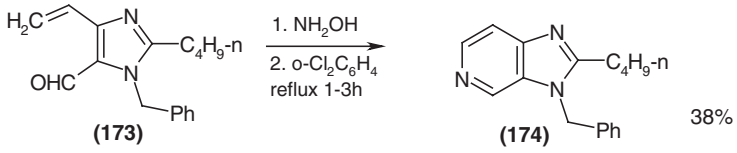
(167) (168)

p-TSA catalysed condensation of 4-oxopyrrolidine **169** and 4-cyano-5-amino-1-*n*-amylimidazole **170** carried out by heating the reagents in toluene furnished **171**, which was subsequently cyclized intramolecularly to IP **172** in high yield by first treating **171** with sodium hydride at 0 °C in THF followed by boiling in toluene in the presence of cadmium chloride (95JOC5243).



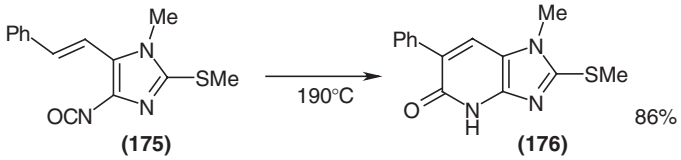
(169) (170) (171) (172)

Imidazoles **173** with vinyl and aldehyde or keto group in positions 4 and 5, respectively, were transformed into IPs **174** by pyridine ring closure on treating **173** with hydroxylamine and subsequently boiling the intermediate oxime in *o*-dichlorobenzene (95H161).

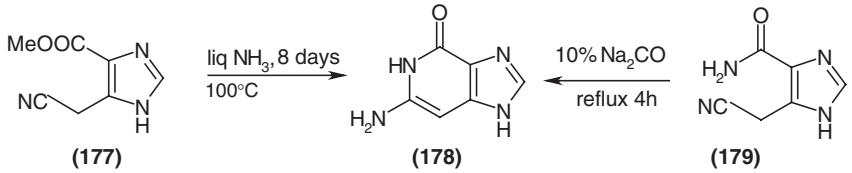


(173) (174)

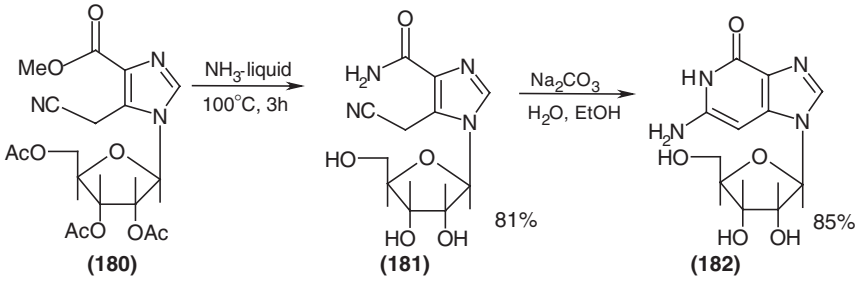
IP **176** was reported to be similarly synthesized from 2-methylthioimidazole **175** containing isocyano and styryl (or propenyl) groups at positions 4 and 5 on heating in dichlorobenzene (93JOC7952).



A unique synthesis of 3-deazaguanine **178** and its ribosyl derivatives was reported by Cook et al. (75JA2916, 76JA1492, 77BRP1474299). The heterocycle **178** was obtained either by prolonged heating of 5-cyanomethylimidazole-4-carboxylic acid **177** with liquid ammonia or by boiling amide **179** with an aqueous solution of sodium carbonate in a sealed tube.



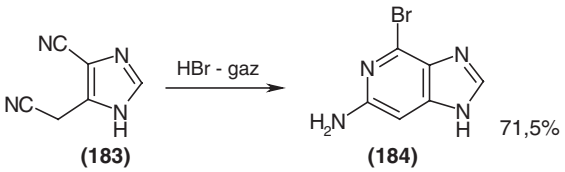
By the same procedure 3-deazaguanosine **182** was prepared from ribosylimidazoles **180** and **181** (75JA2916, 76JA1492).



This method was also used to prepare 3-deazaguanine 2-deoxyribofuranosides from substituted imidazoles (83JMC286).

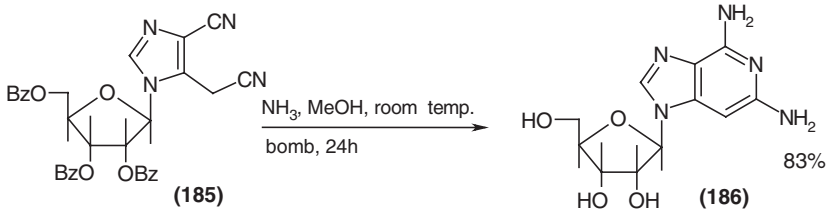
Though deazaguanines **178** and their ribosyl derivatives **182** and its 3-isomer were obtained from imidazoles in high yields, the latter were not widely used as starting compounds due to their difficult and multi-stage preparation.

4-Bromo-6-amino-IcP **184**, a known valuable intermediate substance in the synthesis of 3-deazaguanine thio- and selenium analogues, and also used in the preparation of unavailable 6-amino-IcP, was obtained on saturation of an ether solution of 4-(5)-acetonitrile-5(4)-cyanoimidazole **183** with hydrogen bromide at $-30\,^{\circ}C$ (74JHC233).



(183) (184)

4-Bromo-6-amino-IP ribofuranoside derivatives were obtained in a similar manner from the appropriately substituted imidazoles (78JOC289). 3-Deaza-2,6-diamino-purine 9-β-D-ribofuranoside **186** was obtained by keeping a mixture of imidazole **185** and ammonia in methanol at 0 °C. This procedure facilitates the removal of the protective benzoyl groups in the ribofuranoside moiety of the product (78JOC289).



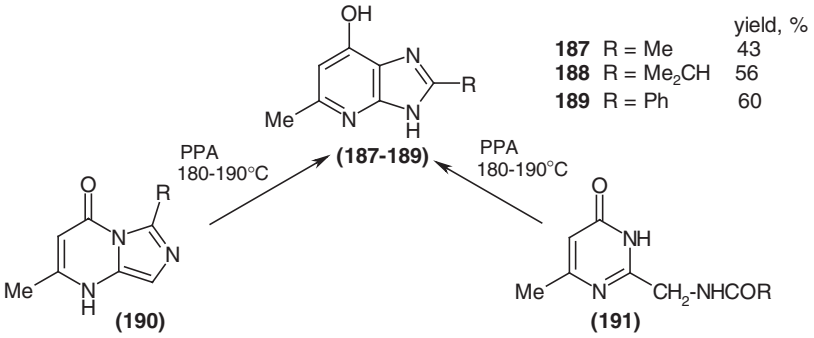
(185) (186)

The synthesis of a phosphonomethoxyethyl derivative of 3-deazaguanine (93CCC1419) was accomplished by a known procedure (76JA1492).

C. Syntheses from Other Heterocycles and Acyclic Precursors

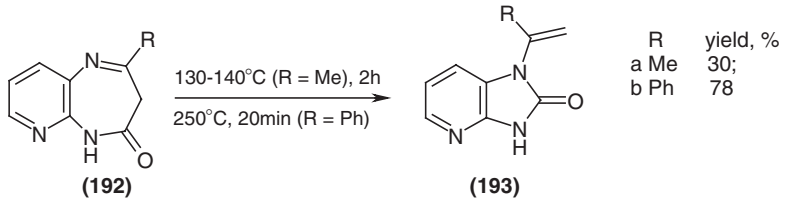
These methods are not numerous, but are sometimes interesting from a theoretical and preparative viewpoint. Albert et al. in the course of their classical research on the reactions of active methylene reagents with pyrimidines (73JCS(P1)1615, 73JCS(P1)1620, 73JCS(P1)1625) revealed that purine **3** when treated with malono-nitrile was converted into the hard-to-prepare IP derivative (5-NH_2-6-CN-IbP) (73JCS(P1)1794).

Substituted imidazo[1,5-a]pyrimidines **190** suffer a ring transformation to give the corresponding 4-hydroxy-5-methyl-IbPs **187**–**189** when heated in PPA. However, compounds **187**–**189** can also be obtained from the more accessible appropriately substituted pyrimidine-4-(3H)-ones **191** and PPA (82JOC167).



(190) (191)

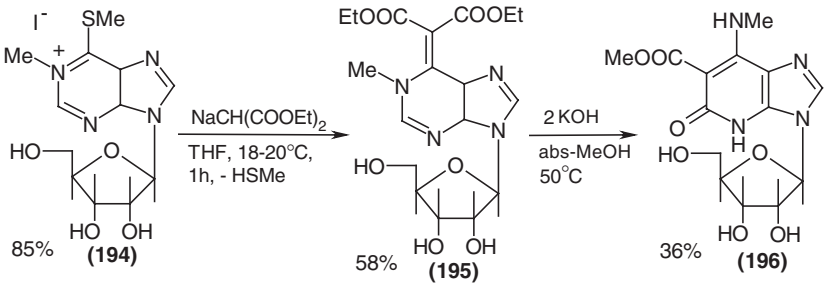
Pyridodiazepinones **192** undergo on heating a rearrangement into IbP-2-ones **193** (68RZC1641, 69JHC735, 69RZC573, 69RZC979).



(192) (193)

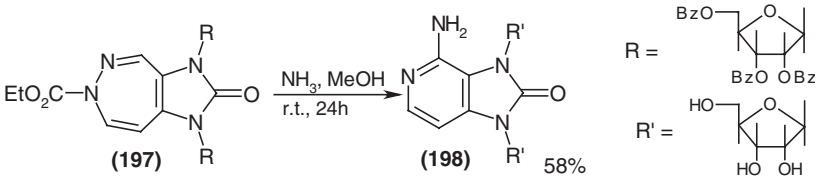
The isomeric pyridodiazepinone when subjected to dry fusion was converted into IcP-2-one in nearly 100% yield (71JHC797).

The 6-bis(ethoxycarbonyl)methylene derivative of 9-ribosylpurine **195** obtained by condensation of 6-thioinosine 1-methiodide **194** with diethyl sodiomalonate underwent a Dimroth rearrangement to afford 3-β-D-ribofuranosyl-IbP **196** derivative on heating in methanolic potassium hydroxide (81H1049).



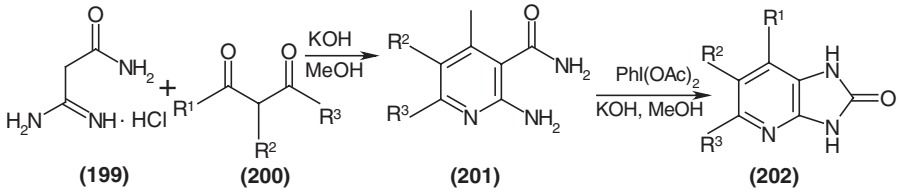
(194) (195) (196)

The benzoylated diribonucleoside of 6-ethoxycarbonyl-1,3-dihydro-imidazo[4,5-d][1,2]diazepin-2-one **197** treated with ammonia in methanol not only suffered deprotection of the benzoyl protective groups but also rearranged into IcP **198** derivative (86T1511).



(197) (198)

In (94TL5775) a synthesis of IbP **202** by condensation of malonamidine hydrochloride **199** and 1,3-dicarbonyl derivative **200** involving the substituted 2-aminonicotinamide **201** intermediate that then underwent a Hofmann rearrangement (94TL5775) was reported.



(199) (200) (201) (202)

III. Physical Properties of Imidazopyridines

A. Spectra of Imidazopyridines

Elguero et al. carried out a detailed analysis of the PMR spectra of IbP and its 1-, 3- and 4-methyl-substituted analogues (72BSF2916). Lindon et al. (86MRC55) examined the ^{1}H-, ^{13}C- and ^{15}N-NMR spectra of neutral and protonated forms of IcP.

Dynamic conformation and exchange effects in 2-(pyridyl-4)-IbP molecules have been studied by PMR spectroscopy. Analyses of the PMR spectra were also carried out for 2-(pyridyl-2, pyridyl-3, 6-methyl- and 5-ethylpyridyl-2)-substituted IcPs, as well as for di(1-methyl-IcP-2-yl) (89KG940). The PMR spectra of 1-, 3- and 5-benzyl IbP derivatives (including those with substituents in the *para*-position of the benzene ring), and also for IcP substituted with 2-cycloalkylaminomethyl groups were described (71LA158).

In a number of studies, PMR spectra were used to solve structural problems, e.g. to determine the position of substituents on the IP rings or to evaluate the general structure of a product (64CPB866, 81MI4, 81H1049, 86KG97, 89JHC289, 94JHC453, 94ZOR460, 94KG1076, 95ZOR304, 96ZOR586, 98ZOR1420, 99JOU583), or to establish the conformation of IP N-glycosides (73UKZ274, 74UKZ258, 81UKZ867).

IR spectroscopy was extensively used mostly to solve particular problems as, for example, the binding of the carbonyl group in 2-formyl-IPs (71AJC2389, 75KG1389), or the tautomerism of 2-amino and 2-thio-3-methyl-IbP (75KG90). With the use of IR spectroscopy, the thione structure was confirmed for various substituted IbP and IcP 2-thiones both in the crystalline state and in CCl_4 solution (88KG799). Similarly, the presence in certain molecules of a carbonyl (69JHC735) or cyano (75KG1389) group was demonstrated.

UV spectroscopy was used as a diagnostic tool in a number of instances: to examine the basicity and to determine the position of protonation in IcP and its derivatives (66JCS(B)285), to examine tautomerism in 2-amino- and 2-mercapto IbPs (75KG90), to compare IbP with purine and benzimidazole (54JCS2071), to measure the torsional angle of the nitro group in an IbP derivative (94KG1071), to elucidate the sites of glycosylation of IbP and IcP (63JOC1837), to study the optical properties of IcP-derived dyes (71KG693), as well as to prove the structures of synthesized IbP and IcP derivatives (66JCS(C)80, 89KFZ697).

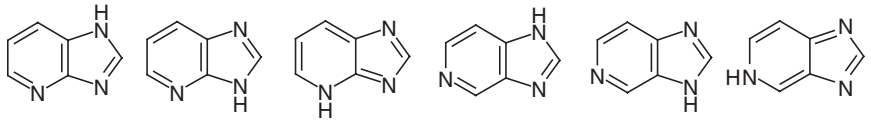
IV. Chemical Properties and Transformations

The chemical behaviour of IPs is determined not only by the chemical properties of the imidazole and pyridine rings separately, but also by intramolecular interaction effects (electronic and steric) that arise between the rings in the fused systems. These effects strongly depend both on the electronic condition of the substrate (neutral molecule, cation or anion) and on the geometrical orientation of the rings. IP's behaviour in various reactions will be considered below. We will also examine the behaviour of related heterocycles (for example, pyridine, isoquinoline or triazolo [4,5-c]pyridine, etc.) to illustrate the general or particular character of the IP's properties.

Primary consideration must be given to a description of tautomerism and relative basicity of the nitrogen atoms in IPs, because many reactions depend on these characteristics.

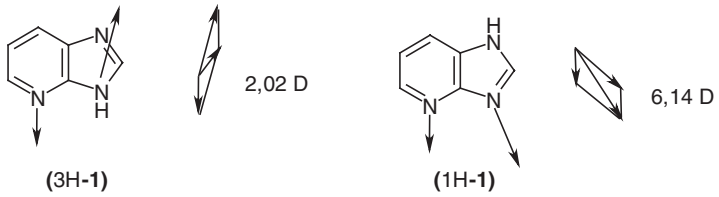
A. Tautomerism of Unsubstituted Imidazopyridines

Only one of the possible tautomeric forms is likely to dominate for each IbP and IcP molecule due to their electronic and geometric asymmetry.



A comparison of the UV spectra of IbP **1** with those of its N-methylated derivatives simulating fixed tautomers (1-methyl- or 3-methyl-IbP) in neutral solvents (cyclohexane, alcohol) is not sufficient for a confident conclusion on the predominant tautomeric form of IbP molecule existing in solution, because the difference in spectra of various tautomeric forms is negligible (71KG1436). The same is true for comparison of the spectra of IcP and 1- and 3-methyl-IcPs.

The approach based on a comparison of dipole moments (d.m.) of IbP **1** and its N-methyl analogues as models of tautomeric forms proved to be useful. Preliminary estimation of the d.m. for 1-H and 3-H forms of IbP calculated by summing the known d.m. of pyridine (2.21 D) and imidazole (4.01 D) (71 MI3) gave a resulting d.m. value of 2.02 D for 3H-IbP and 6.14 D for 1H-IbP. That is, proton migration from N-3 to N-1 in IbP is accompanied by a reorientation of the resultant moment and a sharp increase of d.m. value (the difference is 4.12 D). Calculations using the accepted bond moments gave a total d.m of ~6 D for 4-methyl-IbP.



(3H-**1**) (1H-**1**)

The d.m. values measured for 3-methyl- and 1-methyl-IbP in benzene are 1.85 and 5.78 D, respectively.

The good agreement obtained between the measured and calculated d.m. (taking into account the N-methyl group d.m.) is evidence of a slight reciprocal polarizable interaction between the imidazole and pyridine rings. This confirms the adequacy of the chosen method used for the calculation of the resultant d.m. for IbP.

Finally, the experimental d.m. for IbP **1** is 1.99 D (in benzene), close to the calculated value for 3-H-IbP, distinguishing it from that for 1-H-IbP. Therefore, IbP **1** in benzene solution at 25 °C (68MI1) occurs predominantly (no less than 96%) in the 3-H form (71KG1436, 76AHCS(1)529), which corresponds to the purine 9-H form (54JA6073). The tautomerism of IbP was reported by Elguero and co-workers (72BSF2916), where they gave reference to (71KG1436). They also reported on the tautomerism of IbP, which was observed by ^{1}H-NMR spectroscopic measurements of IbP and *N*-methyl-IbPs in deuterated solvents (chloroform, acetone and DMSO). They showed that the 4-H-IbP form is not present in solution, whereas both the 3-H and 1-H forms are present.

The difference in the calculated d.m. values for IcP 3H- and 1H-forms (2.79 and 4.96 D) obtained according to the above method (92UP1) is less pronounced than for IbP. Consequently, the determination of the predominate tautomeric form should be less accurate here. The low solubility of IcP in benzene precluded its direct determination. Attempts to determine IcP d.m. in *p*-xylene, a better solvent for IcP, were undertaken, but unfortunately the concentration range was still insufficient for extrapolation of its molecular polarization to zero concentration (92UP1). More accurate data could have been obtained by increasing their solubility in benzene or even better in hexane by attaching a saturated hydrocarbon chain of sufficient length (C_5–C_{16}, at C-2 or other C-atoms) and then by measuring the d.m. of the 4-alkyl-IbP and 5-alkyl-IcP.

Lindon et al. (86MRC55) studied the tautomerism of IbP and IcP by NMR spectroscopy. They examined the ^{15}N chemical shifts of these compounds in D_2O, starting with acidic media and gradually moving to basic ones. The tautomeric ratio of 3H- and 1H-forms was estimated to be 70:30 for IbP (1-deazapurine). The approximate difference between their energies was about 2.0 kJ/mol. However, in D_2O, IcP was observed to have an inverse ratio of 1H- and 3-H tautomers (30:70). The estimations were reported to be rough.

Thus, IbP as well as IcP apparently correspond to the 9-H form of purine, the latter being predominant in solutions (54JA6073, 82JA3162).

The 1H-form is more likely for 7-nitro-IbP in DMSO due to its stabilization by an intramolecular hydrogen bond with the NO_2 group (96HCA169).

It was also assumed in (87AX(C)1937) that the 1H-form was stabilized due to an intramolecular hydrogen bond with the methoxy group of the 2-(2-methoxy-4-methylthio)phenyl substituent of IbP. However, a similar bond is presumable to exist also in the 3H-form, and it is not clear why the preference is given to the 1H-form.

B. Ionization Constants and Relative Basicity of N-Atoms in Imidazopyridine Molecules

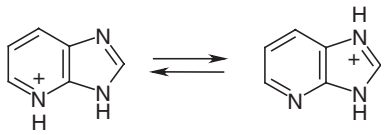
Unsubstituted IPs are amphoteric compounds with ionization constants (pK_a) 11.08 (deprotonation), 3.95 (protonation) for IbP (54JCS2071) and 10.88 (deprotonation), 6.10 (protonation) for IcP (56JCS4683) .

IP's basicity is evidently at variance with the basicity of the imidazole ($pK_a = 6.95$) (55JA5488) and pyridine ($pK_a = 5.23$) (48JCS2240) whose rings constitute imidazopyridine. The basicity of N-methyl-substituted IPs changes over a wide range ($pK_a = 3.93$–3.95 for 3-Me-IbP, 4.10 for 1-Me-IbP, 6.10 for 3-Me-IcP and 6.26–6.45 for 1-Me-IcP) (63JOC1837).

Since the basicity of imidazole is higher than that of pyridine, it is likely that IPs should first be protonated at the imidazole N-atom. But this is not always true.

For example, Barlin (66JCS(B)285) observed that in 6-chloro-IcP the imidazole N-atom was protonated. This is understandable if we take into account the low basicity of 2-chloropyridine. However, recently, the analysis of the ^{13}C-NMR spectra of IcPs led Barlin and Fenn to the conclusion that unsubstituted IcP and its 1- and 3-methyl derivatives were protonated at the N-5 atom in the pyridine ring (81AJC1341). Having thoroughly studied ^{1}H-, ^{13}C-, and ^{15}N-NMR spectra, Lindon et al. found that IcP were protonated exclusively at N-5 (pyridine ring), and the protonation of IbP occurred essentially in a 1:1 ratio at the N-4 atom and at the imidazole ring (86MRC55). In the salt, there are equal concentrations of forms **203** and **204**.

The same equilibrium was observed by Yutilov et al. when studying the UV spectra of IbP in an acid medium (74MI1).



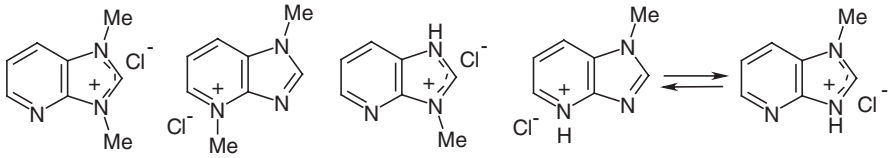
(203) **(204)**

The site of nitrogen protonation in IPs was estimated by measuring the UV absorption spectra of IPs and their N-methylated derivatives in neutral and acidic solutions over a wide pH range and comparing them with the UV spectra of model compounds, monoquaternary IP salts of definite structure.

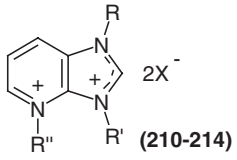
The UV spectra of IbP **1**, 3- and 1-methyl-IbPs **41** and **228** in a neutral solvent (alcohol) possessed two absorption bands. The shape, λ_{max} (nm), ($\log \varepsilon$) of the long-wavelength bands were practically identical for three compounds **1**:288 (3.88), **228**:290 (3.98), and **41**:284 (4.02). But the short-wavelength band had a particular character for each compound. Whereas the short-wave bands of compounds **1** and

41 were well pronounced ($\lambda_{max} = 244$ nm, $\log \varepsilon$ 3.56 and $\lambda_{max} = 252$ nm, $\log \varepsilon$ 3.73), the corresponding band in the spectrum of base **228** was not clearly defined, being overlapped with a flat and long shoulder of the long-wave band ($\lambda_{max} \sim 252$ nm, $\log \varepsilon$ 3.66).

In diluted hydrochloric acid solutions (0.01 N, 0.1 N HCl) and in 3 N HCl the spectra of compound **41** has two distinct absorption maxima at 236, 276 and 282 nm, and $\log \varepsilon$, respectively, 3.69, 4.07 and 4.01. The spectrum is very similar to the UV absorption for imidazolium salt **205**, recorded in alcohol (λ_{max}(nm), ($\log \varepsilon$): 242 (3.61); 274 (3.95); 282 (3.89)). At the same time, the spectrum of 1,4-dimethylimidazo[4,5-b]pyridinium chloride **206** ($\lambda_{max} = 292$ nm, $\log \varepsilon$ 4.03) dramatically differs both from that of chloride **205** and of base **41** recorded in acidic solutions at low concentration. The UV spectra of compound **228** in solutions of low acidity are quite similar to those of pyridinium salt **206,** but differ considerably from that of imidazolium salt **205**. The spectrum of unsubstituted IbP **1** in the acid of low concentration is similar to that of base **228** in the same medium. This suggests that IbP **1** and its 1-methyl derivative **228** in 0.01–3 N hydrochloric acid are protonated at the N-4 atom (pyridine ring) (structures **207** and **208**), whereas 3-methyl-IbP **41** is protonated at the imidazole nitrogen (structure **205**). The presence of a short-wavelength band in the 230–250 nm region ($\log \varepsilon$ 3.1–3.4) in the UV spectra of **1** and **228** at low acidity, uncommon for the spectrum of pyridinium salt **206** but typical for that of imidazolium salt **205**, reveals the pyridinium and imidazolium salts **208** and **209** existing in virtually equal concentrations at equilibrium.



The UV spectra of compounds **1**, **41** and **228**, as well as those of salts **205** and **206** in strong acids (sulphuric acid from 12 to 19.5 N) become practically indistinguishable (λ_{max} (nm), 238–244 and 280–282, $\log \varepsilon$ respectively ~3.72 and 4.1) demonstrating the formation of similar dications **210**–**214** (74MI1).

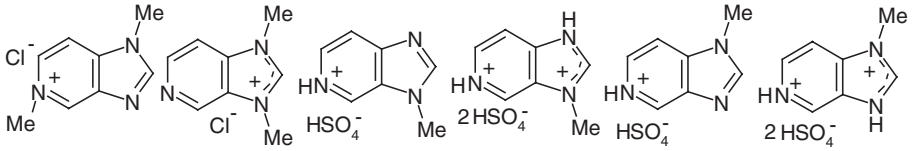


	R	R'	R''
210	H	H	H
211	H	Me	H
212	Me	H	H
213	Me	Me	H
214	Me	H	Me

X = HSO_4

The protonation sequence of nitrogen atoms in IcP **2** was studied within a wide range of acidity in the same way. The UV-absorption spectrum of compound **288** in 0.01 N H_2SO_4 possessed absorption maxima with a red shift of 10–15 nm as compared to that in 0.1 N alkali. The spectrum is similar to that of quaternary

pyridinium salt **215** and is quite unlike the spectrum of imidazolium salt **216**, thus demonstrating that the first proton adds to the N-5 atom of 3-methyl-IcP **288** to give salt 2**1**7. On further increases in H_2SO_4 concentration to 3.7 M (~30%), a gradual shift of both absorption bands is observed in the spectrum of IP **288**. The spectrum of **288** does not undergo any changes in 30–96% solutions of sulphuric acid indicating a total conversion into its dication **218**. It was shown analogously that 1-methyl-IcP **86** also afforded monocation **219** in 0.01 M H_2SO_4 and at concentrations of H_2SO_4 30% and higher, the base **86** was completely converted into dication **220** (75UP).



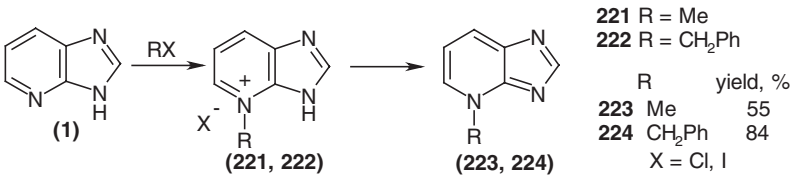
(215) **(216)** **(217)** **(218)** **(219)** **(220)**

C. Quaternization

Except for 3-methyl-IbP **41**, the pyridine ring nitrogen atom is known to be the most basic in IPs, e.g., in compounds **1, 2, 86, 228** and **288**. Therefore, it is of great interest to learn whether IP quaternization occurs at this site.

1. *Salts of Imidazo[4,5-b]pyridines*

Unsubstituted IbP **1** easily takes up methyl iodide in acetone at 30–40 °C to afford pyridinium salts **221** and **222** (94KG1232) that are transformed into the 4-methyl-4H-IbP **(223)** (72BSF2916) in 49% overall yield when treated with alkali. The same base **1** reacts with benzyl chloride in a similar manner to give pyridinium salt **222** that upon treatment with alkali gives rise to free base 4-benzyl-4H-IbP **224** (86ZOR445).



(1) **(221, 222)** **(223, 224)**

221 R = Me
222 R = CH_2Ph

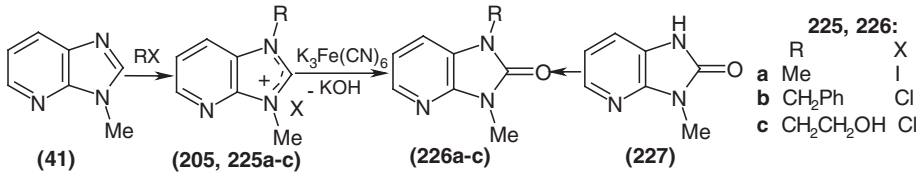
R	yield, %
223 Me	55
224 CH_2Ph	84

X = Cl, I

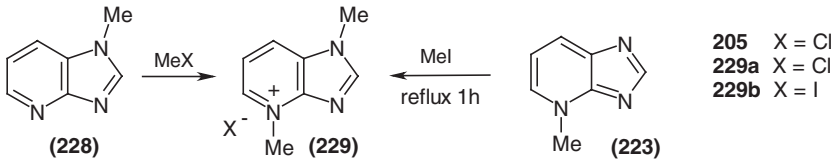
The formation of 3-ethyl-2-methyl-IbP reported in (46JPJ31) seems rather doubtful in view of the above. We believe the product is 4-ethyl-2-methyl-IbP.

3-Methyl-3H-IbP **41** ($pK_a = 3.94$) is the least basic among the *N*-methyl-IPs. It reacts with MeI at 40 °C to give imidazolium salt **205** in 84% yield. The same **41** with MeCl provides salt **225a** at 100–120 °C in nearly quantitative yield; with benzyl chloride it furnishes chloride **327b** in 83% yield, and with ethylene chlorohydrin it gives chloride **327c** in 88% yield. Halides **205** and **225a–c** have similar UV spectra.

Compounds **205** and **225** were shown to be imidazolium salts by oxidation with potassium ferrocyanide in alkali to give IbP-2-one, e.g., **226a, b**, in 50 and 65% yield, respectively. The latter were prepared by an independent synthesis through methylation or benzylation of imidazolone-2 in alkali (yields 55 and 75%, respectively) (68KG954).

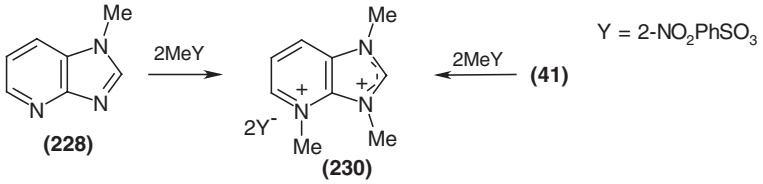


As distinct from compound **41** its isomer, 1-methyl-1H-IbP **228,** with MeCl and MeI forms monoquaternary salts **229** in 97–98% yields. Its properties are quite different from those of halides **205** and **225** indicating that they have the structure of 1,4-dimethylimidazo[4,5-b]pyridinium iodide and chloride **(229a, b)** (73KG570). *N*-methyl isomers, 4-methyl-IbP (**224**), quantitatively add MeI in alcohol to afford salt **229b** exclusively (94KG1232).



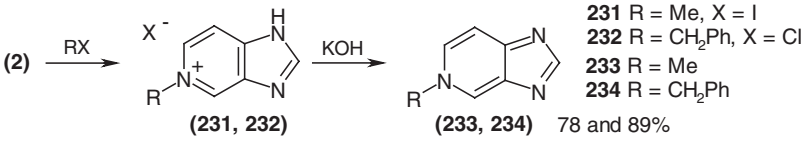
Based on an analogy with the above data (68KG954) on the quaternization of base **41,** the product obtained from methyl *o*-nitrotosylate and 1,2-dimethyl-IbP was erroneously described as an imidazolium salt (71KG1561). It was apparently 1,2,4-trimethylimidazo[4,5-b]pyridinium *o*-nitrotosylate.

Finally, the fusion of bases **41** or **228** with two equivalents of methyl *o*-nitrobenzenesulfonate at 140–150 °C (74MI1) furnished the same product (disalt **230**) in 90–95% yield.

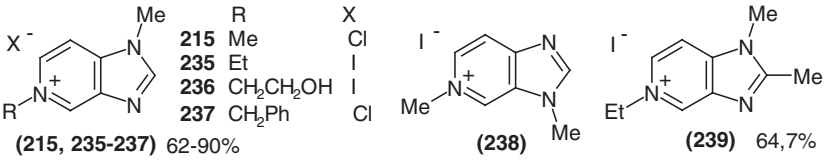


2. *Salts of Imidazo[4,5-c]pyridines*

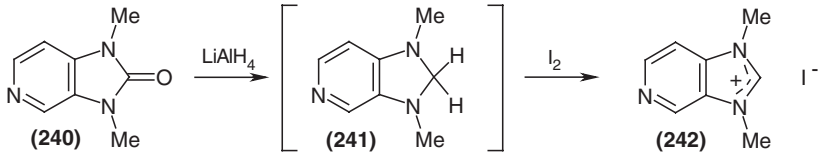
IcP **2** readily undergoes quaternization by MeI or $PhCH_2Cl$ at 40–70 °C to give salts **231** and **232** in 72 and 78% yields, respectively. The latter can be easily transformed into bases **233** and **234** by treating them with excess concentrated alkali (86ZOR445).



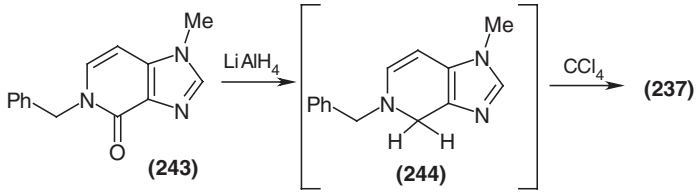
Monoquaternary salts **215**, **235–239** are readily formed from alkyl halides and 1-methyl-IH-IcP **86**, 3-methyl-3H-IcP **288** and 1,2-dimethyl-IcP **86** (70KG228, 78MI4, 89KFZ56).



The structure of salts **215** and **235–239** was elucidated by a comparison of their properties with those of the known imidazolium **242** and pyridinium **237** salts. The synthesis of iodide **242** was carried out by reducing imidazolone **240** (94KG1071) with lithium aluminium hydride to give dihydro-IP **241** followed by oxidation of the latter with iodine (78MI4).

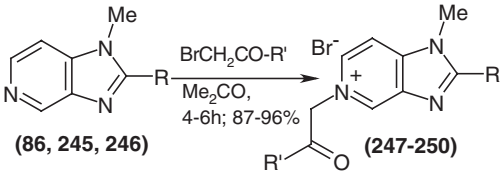


By the same procedure, dihydropyridine **244** was obtained from pyridone **243**, prepared by oxidation of pyridinium salt **237** (78MI6).



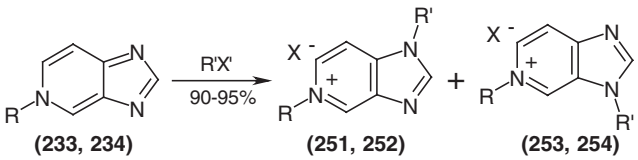
Taking into account that the properties of methiodides obtained from bases 1-methyl-IcP **86** and 3-methyl IcP **288** differ greatly not only from each other but also from the imidazolium salt **242,** their structures were assumed to be those of pyridinium salts **235, 236** and **238**. On the other hand, iodide **235** and quaternary salts **215** and **235** have similar UV spectra and this suggests their structures are that of *N*-5-alkyl halides. Samples of chloride **237** obtained by quaternization of **86** and by an alternative procedure from pyridone **243** proved to be identical (78MI4).

IcP **86** and its 2-substituted derivatives **245** and **246** with bromomethyl ketones at room temperature in acetone gave the corresponding 5-acylmethyl salts **247**–**250** (89KFZ160).



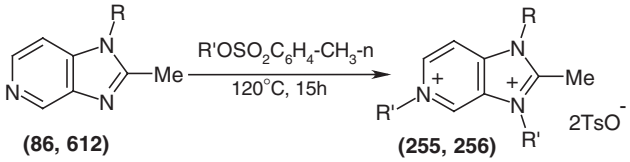
	R	R'	yield, %
247	3,4-$(MeO)_2$Ph	Ph	90
248	3,4,5-$(MeO)_3$Ph	CMe_3	90
249	H	3,4-$(MeO)_2$Ph	95
250	H	n-BrPh	94

The quaternization of 5-methyl- and 5-benzyl-IcP **233** and **234** on treating with MeI and benzyl chloride afforded pyridinium salts **251, 252** and **253, 254** in a 3:2 ratio (according to PMR) (98UP2).



	R	R'	X
251	Me	Me	I
252	CH_2Ph	Me	I
253	Me	CH_2Ph	Cl
254	CH_2Ph	CH_2Ph	Cl

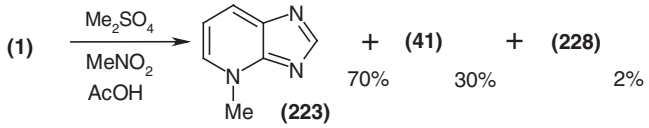
IcPs more readily afford bisquaternary salts as compared to IbPs. For example, 1,3,5-trialkyl(dialkylphenyl)imidazolio[4,5-c]pyridinium ditosylates **255** and **256** were obtained by fusion with toluene sulphonic acid esters of 1,2-dimethyl- **86** or 1-phenyl-2-methyl-IcP **612** (70KG228, 71KG693), or of a mixture of *N*-monomethyl IcP derivatives (72KG683).



	R	R'	yield, %
255	Me	Me	100
256	Ph	Et	91,8

D. N-Alkylation

Methylation of unsubstituted IbP **1** by dimethyl sulphate, described by Mizuno et al. (63JOC1837), was carried out in nitromethane and acetic acid under heating. The isolation and purification of the products was made through picrates. The authors believed that they obtained two substances: 3-methyl- and 1-methyl-IbP. Later Elguero et al. repeated this experiment using another isolation procedure, column chromatography. The PMR spectra proved that 4-methyl-IbP **223** (70%) was the main product along with 30% of 3-methyl-IbP **41** and 2% of 1-methyl-IbP **228** (72BSF2916). Elguero et al. were the first to describe 4-methyl-IbP **223**.

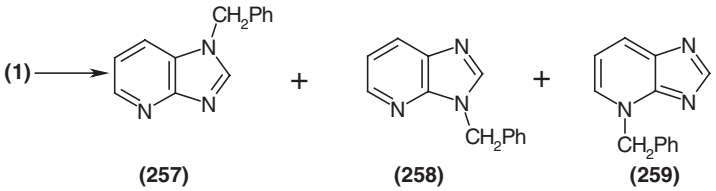


As distinct from quaternization of the neutral base, the N-alkylation of imidazopyridine anions proceeds with alkyl halides.

The alkylation of IbP **1** in an alkaline medium to give the corresponding anion follows another pathway. A mixture of 3-methyl-IbP **41** (in 33–40% yield) and 1-methyl-IbP **228** (in 8–9.3% yield) formed when base **1** was treated with methyl iodide in an alkaline alcoholic solution with cooling. These two substances were quite readily separated because isomer **228** unlike compound **41** formed complexes with silver(I) salts (nitrate or acetate) insoluble in water. The complex was easily decomposed when treated with aqueous ammonia. IbP benzylation by benzylphenyldimethylammonium chloride in alkali gave similar results. Isomers separated as silver salts afforded 3-benzyl-IbP (in 50–52%) and 1-benzyl-IbP (in 15.4–16% yield) (79SUP694511).

The methylation of 6-bromo-7-chloro-IbP by methyl iodide in the presence of K_2CO_3 furnished the 3-methyl derivative in low yield (82JHC513).

Benzylation of IbP **1** in DMF occurred on treating with sodium hydride and benzyl bromide to give a mixture of three possible isomers **257, 258** and **259** in 72% overall yield in a ratio 1:3,6:1,6 (95JOC960).



Under the same conditions benzylation of 2-tetramethyleneaminomethyl-IbP with *p*-chlorobenzyl chloride afforded 3-benzyl-IbP and 1-methyl derivatives in 23 and 7% yield, respectively. 2-Pentamethyleneaminomethyl-IcP treated with 3-benzyl chloride and sodium hydride formed a benzyl derivative, whereas reaction with *p*-chlorobenzyl chloride resulted in a mixture of 1- and 3-substituted salts in low yields (5–7%) (71LA158).

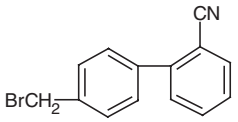
Unsubstituted IcP **2** treated with dimethyl sulphate in aqueous alkali (50%, 20 min) was converted into a mixture of N-methyl derivatives in a quantitative yield (72KG683). 1,2-Dimethyl-1H-IcP was obtained in 20% yield by extraction with benzene.

The benzylation of 4-chloro-IcP with benzyl bromide and its *o*-fluoro derivative in DMF or DMSO in the presence of potassium carbonate gave 1- and 3-benzyl-IPs separated on silica gel (88JHC1255) in poor yields.

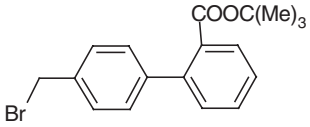
The alkylation of IcP by chloromethyl pivalate in the presence of K_2CO_3 in DMF provided a mixture of 1- and 3-pivaloyloxymethyl derivatives in 7.5:2.5 ratio in 88% overall yield (86T1511).

Substituted *p*-bromomethylbiphenyl **260** benzylated 4-chloro-2-*n*-butyl-IcP in the presence of potassium *tert*-butylate in *N*-methylpyrrolidone (NPM) afforded 3-substituted IcP in good yield (94JMC1632).

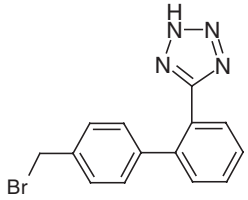
Products of *N*-3-aralkylation were prepared in a very high yield from 2-substituted IPs and complex benzyl bromide derivatives **261** and **262** (91JMC2919, 92MIP4025358).



(260)



(261)

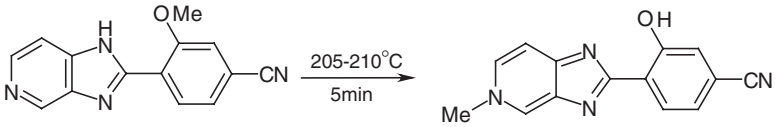


(262)

The reaction of diethylaminoethyl chloride with 6-nitro-IbP furnished a mixture of 1- and 3-substituted IbPs (61USP3004978, 65SWP386442).

Ethyl bromoacetate with 2-(*p*-chloro-phenyl)-IbP 5**6** first treated with sodium hydride gave a mixture of 1- and 3-ethoxycarbonylmethyl derivatives of the parent (91JMC2993).

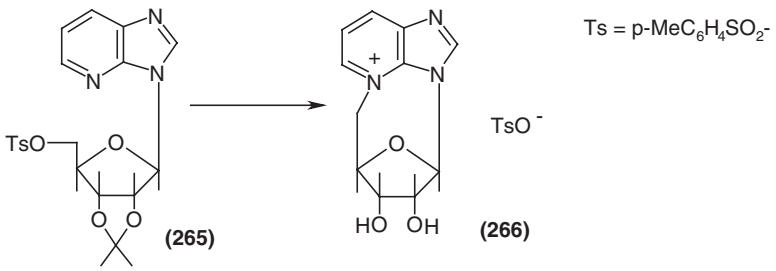
An interesting intramolecular rearrangement of substituted 2-phenyl-IbP **263** on short heating at 200 °C gave product **264** (86TL5997). This reaction was accompanied by methyl group migration to N-5 of the initial IbP.



(263) **(264)**

The following example of a Mannich reaction in the IbP series should be regarded as an N-alkylation: a reaction between 6-chloro-IbP, paraformaldehyde and secondary amines resulted in a mixture of *N*-dialkylaminomethyl derivatives of the initial compound (60CPB539).

Mizuno et al. reported an interesting example of an intramolecular N-alkylation of IbP: 3-*β*-D-ribofuranosyl-3H-IbP 5′-tosylate **265** refluxed in acetone afforded cyclic salt **266** (63CPB265).



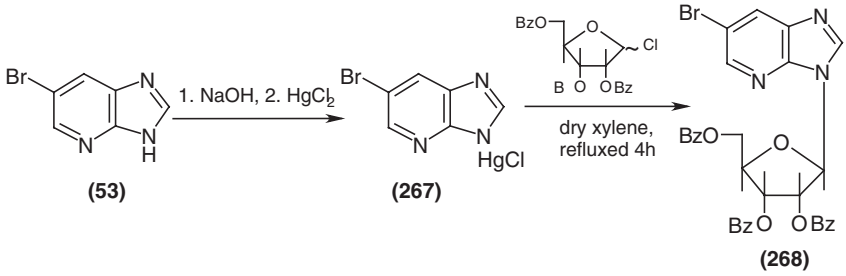
(265) **(266)**

The Elguero group (72BSF2916) described a rare case of IbP **1** arylation by 2,4-dinitrochlorobenzene to give 1-(2,4-dinitrophenyl)-IbP.

E. N-Glycosylation

The introduction of *N*-glycosyl residues into IPs is a special type of N-alkylation providing new powerful medicines of these purine derivatives. The synthesis of 1-and 3-deazapurine nucleosides was reviewed in (81KG147).

Chatterjee et al. were the first to attempt the introduction of a glycosyl moiety onto an IP molecule. An IbP chloromercury salt was treated with *O*-acyl-1-halosugar and subjected further to deacylation to give IbPs (1-deazapurine) containing an *N*-1-glycoside group originating from ribose, xylose, galactose and glucose (60MI1). Mizuno et al. obtained from the same IbP, chloromercury salt and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride (BRC) 3-ribosyl-IbP. Its structure was confirmed by the similarity of its UV spectrum with that of 3-methyl-IbP rather than with that of 1-methyl-IbP (63CPB265, 63JOC1837). The same structure was also assigned to the product **268** obtained from 6-bromo-IP chloromercury salt **267** (prepared from base **53**) and BRC (63IJC30).

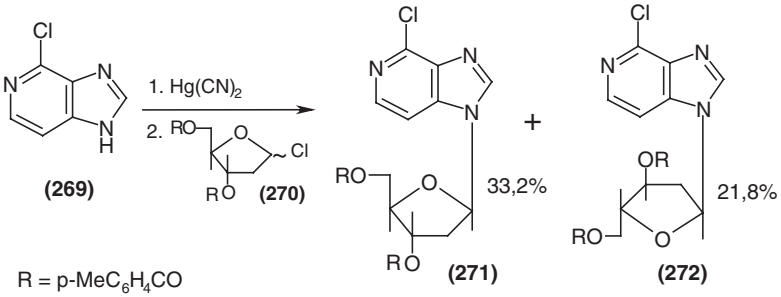


(53) **(267)** **(268)**

However, later, Mizuno et al. reported that this reaction provided not only compound **268** but also the 1-isomer; the total yield reached 100% (65JOC4066).

The above publication contained also data on ribosylation of IbP 4-oxide that led to a mixture of 1- and 3-(2,3,5-tri-*O*-benzoyl-*β*-D-ribosyl)-IbP 4-oxides in 20% and 22% yields, respectively. The same procedure was used to introduce ribosyl residues into 7-acetylamino-IbP at N-3 (66MI1).

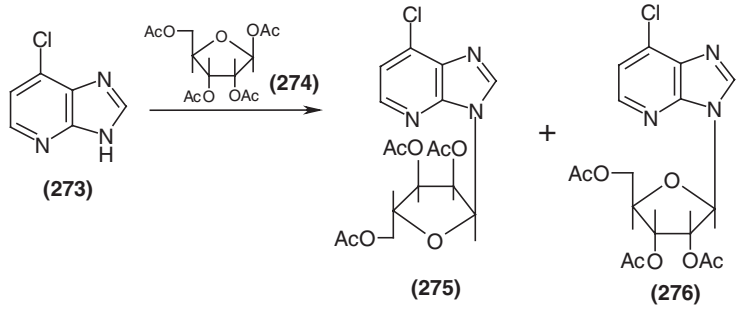
The mercury method proved to be successful for introducing ribosyl moieties into IcP molecules. This procedure was used to obtain 3-ribosyl-IcP and its 7-nitro derivative (63IJC30, 63JOC1837). 4-Chloro-IcP **269** gave rise to 1- and 3-ribosyl derivatives (64JOC2611, 65JOC4066). Another strategy developed by Mizuno et al. can be regarded as a modification of the mercury method. 4-Chloro-IcP **269** was converted to its mercuric salt by heating with mercuric cyanide in nitromethane. Then molecular sieve 4A and 2-deoxy-3,5-di-*O*-(*p*-toluyl)-D-erythropentafuranosyl chloride **270** in nitromethane were added. Following refluxing for 3 h, a mixture of the α- and *β*-anomers of 4-chloro-1-(2-deoxy-3,5-di-*O*-(*p*-toluyl)-D-erythropentafuranosyl)-1H-**271** and **272** were separated (81MI3).



Ribosylation of 4-chloro-IcP **269** by 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride (in 47% yield) (68CPB2011) was carried out in the same way.

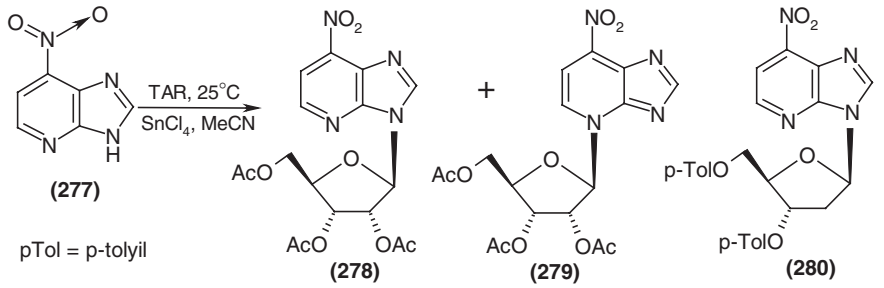
Non-mercury methods of IP's glycosylation were also developed. For example, fusion of 4-chloro-IcP with 1,2,3,5-tetra-*O*-acetyl-*β*-D-ribofuranose in the presence of catalytic amounts of *p*-toluenesulphonic acid at 160 °C (25 mm) for 30 min gave 4-chloro-1-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-1H-IcP in 40% yield (66B756, 66JMC105).

The mixture of α- and *β*-anomers (1:6 ratio) of 7-chloro-3-(triacetyl-D-ribofuranosyl)-IbP **275** and **276** in 41% overall yield (71RTC654) was obtained from tetraacetylribofuranose **274** and 7-chloro-IbP **273**.



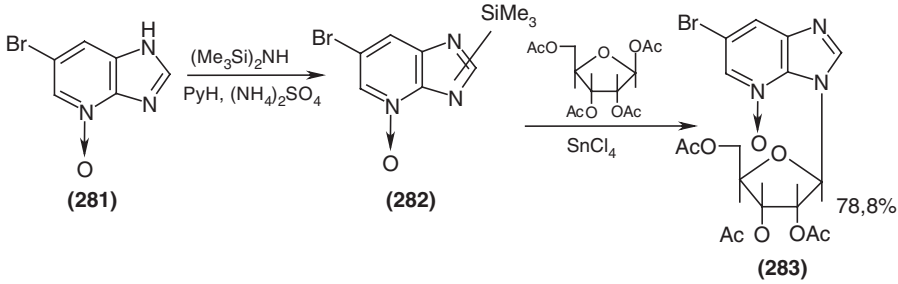
Sodium salts of IPs can be used in glycosylation. Sodium hydride was added to 4-chloro-IcP in DMF, the reaction mixture was heated for 5 min at 50 °C, and then 2,3,5-tri-*O*-benzoyl-D-arabinofuranosyl chloride was added. The mixture at room temperature for 2 h furnished 4-chloro-1-(2,3,5-tri-*O*-benzyl-D-arabinofuranosyl)-1H-IcP in 89% yield (82USP4315000).

Glycosylation of 7-nitro-IbP **277** with 1,2,3,5-tetra-*O*-acetyl-*β*-D-ribofuranose (TAR) and $SnCl_4$ gave a mixture of N-3 and N-4 *β*-isomers **278** and **279** in 87% overall yield. The sodium salt of the same 7-nitro-IbP **277** at 25 °C with 1-chloro-2-deoxy-3,5-di(*p*-toluyl)-D-erythro-pentafuranose in MeCN was converted into a single N-3 *β*-isomer **280** in a good yield (95TL1601).

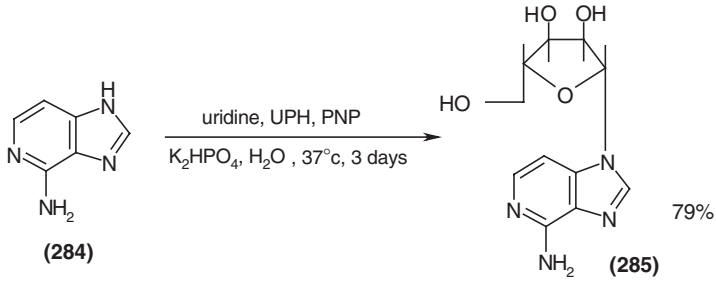


The treatment of 2-deoxy-3,5-di-*O*-(4-toluyl)-α-D-erythro-pentafuranosyl chloride (in MeCN with powdered KOH) with IbP **1**, its 7-chloro derivative **273** or 7-nitro-IbP **277** led to the formation of a mixture of the 1- and 3-pentafuranosyl derivatives (96HCA169).

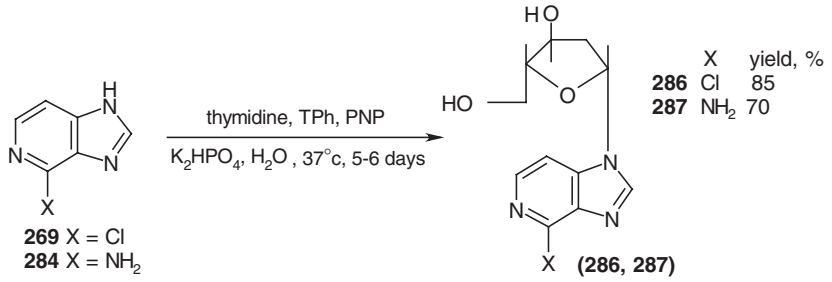
Heating at reflux IbP-4-oxide **281** in a mixture of hexamethyldisilazane and pyridine (1:1 ratio) for 4 h in the presence of a catalytic quantity of $(NH_4)_2SO_4$ provided trimethylsilyl derivative **282** of the parent. Stirring this product with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose and $SnCl_4$ at room temperature for 18 h resulted in a high yield of substituted 3-ribosyl-1*H*-IbP 4-oxide **(283)** (82JHC513).



The enzymatic synthesis of ribonucleosides and 2-deoxyribonucleosides of IcPs is of a special interest. Krenitsky et al. performed direct IcP ribosylation by treating the 4-substituted base with the nucleoside uridine in the presence of uridine phosphorylase (UPH), purine nucleoside phosphorylase (PNP), and potassium hydrophosphates at pH close to 7 (**284** → **285**).

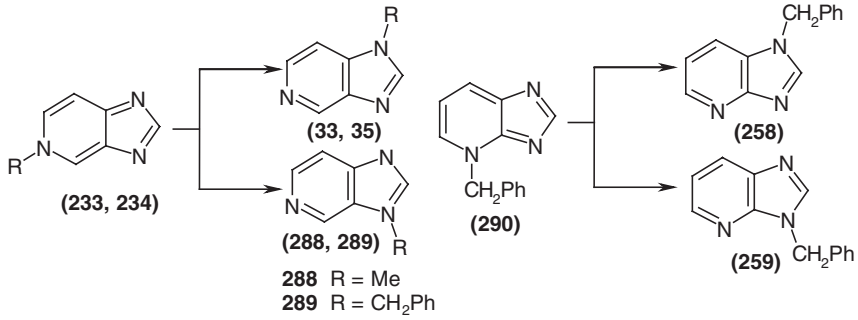


The corresponding 1-(2-deoxy-β-D-ribofuranosyl) derivatives **286** and **287** formed in high yield (86JMC138) by adding thymidine phosphorylase (TPh) and purine nucleoside phosphorylase (PNP) to 4-amino- and 4-chloro-IcP **269** and **284**.



F. Thermal Stability of N-Substituted Imidazopyridines

Bases **233, 234** and **290** were subjected to thermal isomerization at 200–300 °C to afford a mixture of 1- and 3-methyl-IPs or benzyl-substituted IPs **33, 258, 259, 288** and **289** in 90% overall yield. The isomers formed in the following ratio according to GLC and PMR data: **35** and **288**, 1:1; **33** and **289**, 2:1; **258** and **259**, 5:1 (86ZOR445).



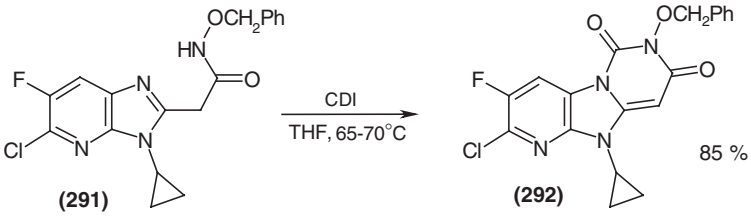
These data illustrate the higher thermal stability of 1- and 3-alkyl-IPs as compared to the corresponding N-4 or N-5-isomers.

G. N-Acylation

IPs are N-acylated with difficulty. When an IP, for example, 6-bromo-2-trifluoromethyl-5-methyl-IbP, is treated with a strong acylating agent (e.g., ethyl chlorocarbonate) in the presence of K_2CO_3 in acetone, a mixture of N-acyl (ethoxycarbonyl) derivatives of the parent base is obtained in a good yield (67SUP207143).

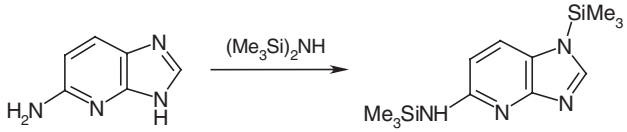
2-Methoxycarbonylamino-IbP treated with isocyanate at room temperature within 48 h afforded an addition product (yield 74%) at the N-3 atom (75USP3920669, 77BRP1465583).

A peculiar tricyclic product **292** is formed when IP **291** is acylated with carbonyldiimidazole (CDI) (94HCA1057).



(291) (292)

Trimethylsilylation of IPs can be regarded as a kind of acylation. Thus, 6-amino- and 6-oxy-IbPs when heated with hexamethyldisilazane afford products of trimethylsilylation at amino- and oxy-groups as well as at the N-1 atom (e.g., **293** → **294**) (66JPR274).



(293) (294)

Silylation of 5-bromo-IbP by trimethylchlorosilane occurs under heating in toluene in the presence of triethylamine to give 1-trimethylsilyl-5-bromo-IbP in a low yield (73UKZ274).

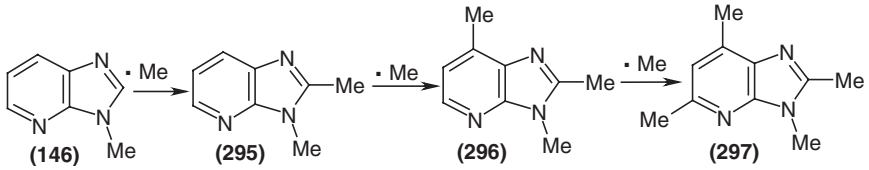
Refluxing for 4 h of IbP-4-oxide with hexamethyldisilazane in pyridine in the presence of $(NH_4)_2SO_4$ catalyst provided a mixture of all possible *N*-trimethylsilyl isomers of the parent base (82JHC513).

H. Radical C-Alkylation

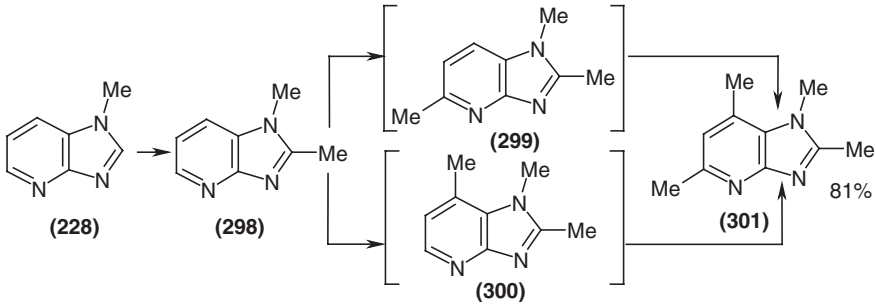
The methods of homolytic alkylation of pyridine and related heterocycles developed by Minisci (73S1, 74AHC123) are used to introduce C-alkyl groups into IP molecules.

Oxidative decarboxylation of acetic acid at 75 °C by $(NH_4)_2S_2O_8$ and silver ions as catalyst in 10% H_2SO_4 containing 3-methyl-IbP **41** led to the formation of a mixture of variously C-methylated IbPs. Gradually increasing the excess of the generated methyl radicals with respect to the substrate first gave a mixture of di- and trimethyl-IPs **295** and **296** (in 71% overall yield), and then 2,3,5,7-tetramethyl-IbP **297** in 6% yield.

The same procedure was used with bases **41** and **295** for C-methylation by catalytic decomposition of *tert*-butylhydroperoxide, but a four-fold excess of the latter in 70% H_2SO_4 produced only tetramethyl-IbP **297** in 81% yield (78MI3).

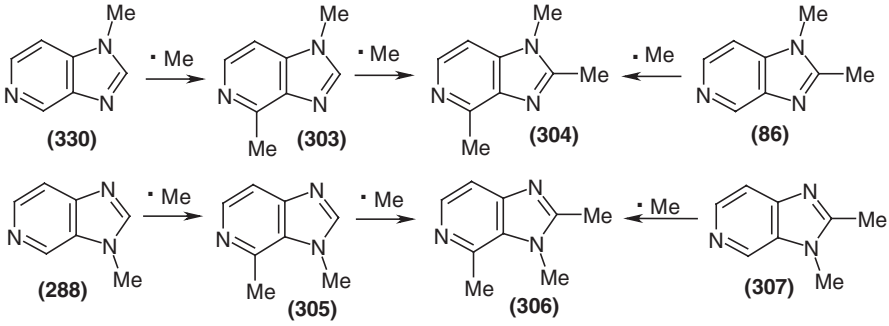


The attempts to methylate 1-methyl-IbP **228** by means of oxidative decarboxylation of acetic acid silver salts failed because this base bound the silver ions into an insoluble complex. However, the catalytic decomposition of *tert*-butylhydroperoxide in 70% H_2SO_4 first provided 1,2-dimethyl-IbP **298**, later converted into a mixture of 1,2,5- and 1,2,7-trimethyl-IbP **299** and **300** isomers that were hard to separate. The final compound is 1,2,5,7-tetramethyl-IbP **301** (78MI3).

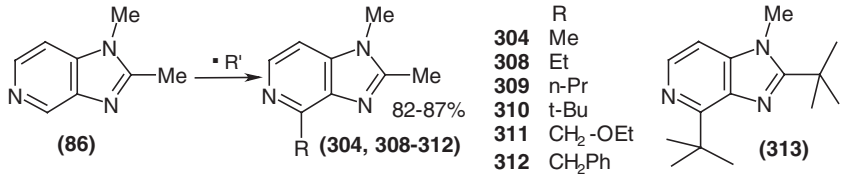


IcP derivatives capture methyl radicals more efficiently and selectively than IbPs. However, as distinct from the latter, IcPs are methylated by a CH_3COOH-$(NH_4)_2S_2O_8$-$AgNO_3$ catalytic system first at the C-4 atom and only then at the C-2 atom. According to GLC data, compounds **303** and **305** (77KG993, 78MI7) formed first from 1-methyl-IcP **330** and 3-methyl-IcP **288**, and only afterwards appeared the trimethyl derivatives **304** and **306**.

In 2-substituted IcP (e.g., **46** and **307**), methylation is known to take place very selectively, giving only **304** and **306** bases in 95% yield respectively (78MI5).

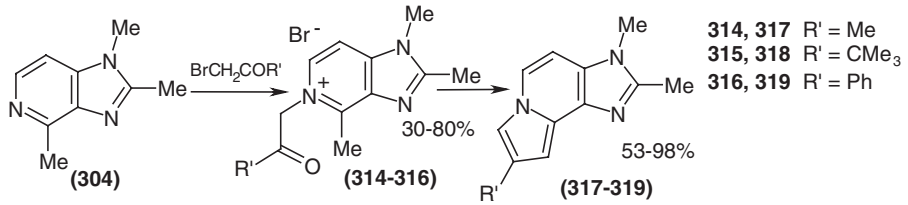


4-Alkyl- and 4-benzyl-substituted IcPs **304**, **308**–**312** were successfully obtained by oxidative decarboxylation of carboxylic acids (78MI5).

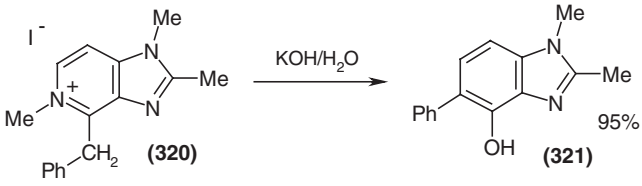


Trimethylacetic acid (oxidizing agent: $S_2O_8 + Ag^+$) and base **330** furnished IP **313** with two *tert*-butyl groups in the molecule (98UP1). By generating oxymethyl radicals [CH_3OH-$(NH_4)_2S_2O_8$] or dioxanyl radicals [dioxane-$(NH_4)_2S_2O_8$] in the presence of base **86**, 4-hydroxymethyl and 4-dioxanyl IP derivatives were obtained in 67 and 60% yields, respectively (78MI7, 86SUP1048744).

In 4-alkyl(benzyl)-IPs, the methyl and methylene groups possess enhanced chemical reactivity that increases greatly in their monoquaternary salts. The quaternization of base **304** by α-bromoketones gave salts **314**–**316** that were converted into imidazo[4,5-g]indolizine **317**–**319** derivatives when treated by bases.

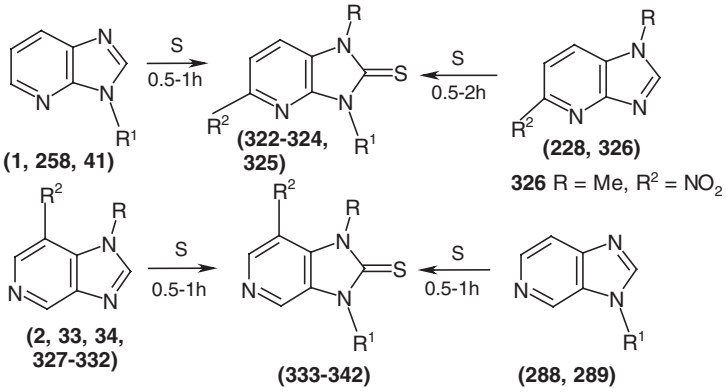


Methiodide **320** heated with an alkaline solution afforded 4-hydroxy-5-phenyl-1,2-dimethylbenzimidazole **321** (87KG995).



I. Thionation

Yutilov and Svertilova (71KG428, 88KG799) revealed that fusion of **1**, **2**, **33**, **34**, **41**, **228**, **258**, **288**, **289**, **326** and **327**–**332** IPs with an equivalent amount of elemental sulphur at 230–260 °C resulted in the insertion of a sulphur atom into the C(2)–H bond of the imidazole ring to form 1,3-dihydro-2H-IP-2-thiones **322**–**325**, **333**–**342**. The products turned out to be identical to the cyclization products obtained by treating the corresponding *o*-DAPs with carbon disulphide.



	R	R^1	R^2	yield, %
322	H	H	H	79
323	H	Me	H	76
324	H	CH_2Ph	H	95
325	Me	H	NO_2	93
327	R = Ph, R^2 = H			
328	R = i-Pr, R^2 = H			
329	R = n-Bu, R^2 = H			
330	R = Me, R^2 = H			
331	R = H, R^2 = Br			
332	R = H, R^2 = NO_2			

	R	R^1	R^2	yield, %
333	H	H	H	80
334	Me	H	H	81
335	i-Pr	H	H	94
336	n-Bu	H	H	82
337	C_6H_{11}	H	H	86
338	CH_2Ph	H	H	94
339	H	H	Br	99
340	H	H	NO_2	99
341	H	Me	H	79
342	H	CH_2Ph	H	98

The difference in orientation of imidazole and pyridine rings in IbP and IcP as well as the character of substituents did not affect the reaction course and the yields of thiones (usually 80–90%), although in some cases, thiones were obtained in quantitative yields (71KG428, 88KG799).

The low solubility of the thiones in solvents used for recording IR spectra prevented their measurement. To impart sufficient solubility, a compound was synthesized with an octadecyl substituent in position 1 of IcP-2 thione. The product was readily soluble in $CHCl_3$ and CCl_4. The IR spectrum of this thione in CCl_4 contained a characteristic strong absorption band at 3456 cm^{-1} belonging to an NH group (88KG799).

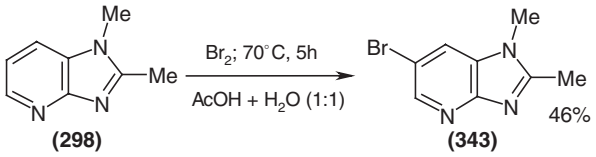
Thus, IPs such as purine (64JOC3209) and benzimidazole (65KG621) are capable of reacting with elemental sulphur to give IP-2-thiones. This reaction is highly selective and can be regarded as the most typical and common for IPs as well as for a whole series of compounds including imidazole, benzimidazole and purine.

J. Halogenation

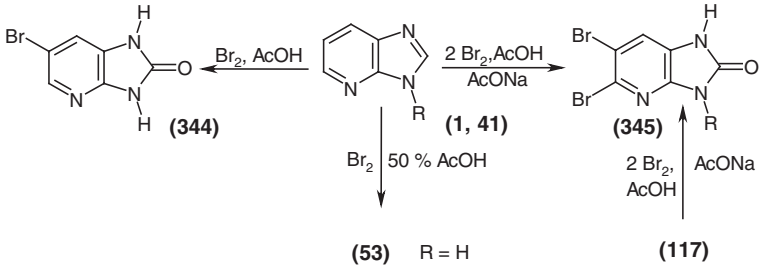
IbPs and IcPs in halogenation as well as in other reactions behave differently and so we consider them separately.

1. *Imidazo[4,5-b]pyridines*

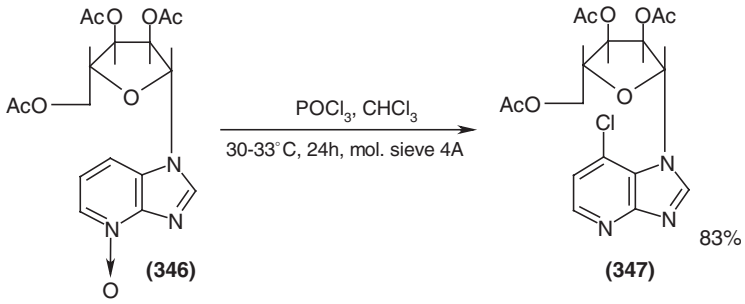
As far as we know, no data have been published on the direct halogenation of unsubstituted IbPs. However, the formation of 6-bromo derivative **343** in a good yield by bromination of 1,2-dimethyl-IbP **298** under relatively mild condition was reported in (71KG279).



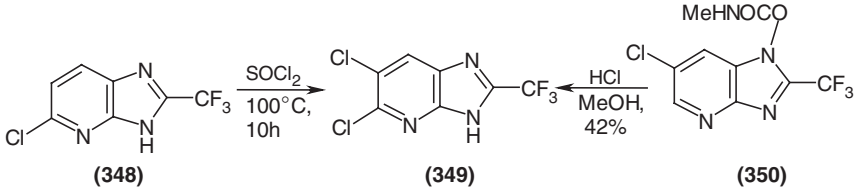
Recently, Yutilov et al. (2003ZOR302) found that both IbP **1** and 3-methyl-IbP **41** on heating with excess bromine in glacial acetic acid in the presence of anhydrous sodium acetate unexpectedly were converted into the corresponding 5,6-dibromo-IbP-2-ones **345** in 31–38% yields. However, treating **1** with bromine in a 1:1 molar ratio gave 6-bromo-IbP-2-one **344**, whereas **1** on bromination in 50% aqueous acetic acid furnished the 6-bromo-IbP **53**, analogous to the conversion of **298** into **343**. The mechanism of these abnormal brominations of bases **1** and **41** was suggested to involve a covalent addition of acetic acid to the C=N bond of the imidazole ring in substrate **1** followed by oxidation with bromine of the resulting 1,2-dihydroimidazole to 2-acetoxyimidazole with subsequent conversion of the last compound to 2-oxy(oxo)-IbP **117** by hydrogen bromide formed in the course of the reaction. Such a compound should readily react with bromine to give dibromo derivative **345** as observed in the bromination of 1,3-dimethyl-IbP-2-one **226a** (98ZOR1420).



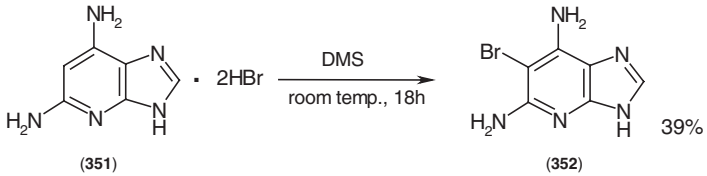
1-Methyl-IbP-4-oxide and 6-bromo-1-methyl-IbP-4-oxide heated to 50 °C with phosphorus oxychloride in chloroform in the presence of molecular sieve 4A gave exclusively 1-methyl-7-chloro- and 1-methyl-6-bromo-7-chloro-IbP in 92 and 86% yields, respectively. However, heating 3-methyl-IbP-4-oxide with $POCl_3$ furnished a mixture of 5- and 7-chloro derivatives of the base in 20% and 40.4% yield, respectively. The same method was used to prepare the corresponding 7-chloro derivative **347** from 1-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-IbP-4-oxide **346** (82JHC513).



1-Hydroxy-2-trifluoromethyl-IbP on treatment with thionyl chloride in DMF afforded 5-chloro-2-CF_3-IbP **348**. Introduction of a 1-hydroxy group into this compound and repeated treatment with $SOCl_2$ led to the formation of 5,6-dichloro-2-trifluoromethyl-IbP **349**, which was also obtained independently from 6-chloro-1-methylcarbamoyloxy-2-trifluoromethyl-IbP **350** by heating in a methanolic solution of hydrogen chloride (76SUP535908).



An unusual formation of 6-bromo-5,7-diamino-IbP **352** was observed when 5,7-diamino-IbP dihydrobromide **351** was kept at room temperature in DMSO solution for a long time (73JOC613).

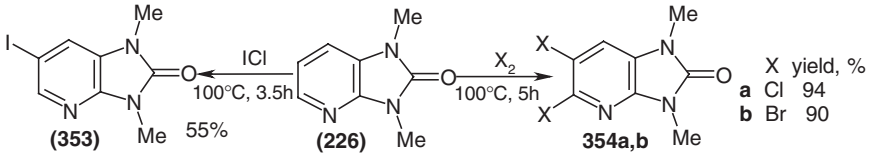


The action of an oxidizing agent ($KClO_3$) on a solution of 5-chloro-3-diethylaminoethyl-IbP-2-one in concentrated HCl led to the introduction of the second chlorine atom to give 5,6-dichloro-3-diethylaminoethyl-IbP-2-one in a relatively low yield (79BRP2006758, 81USP4247556).

A direct treatment with chlorine and bromine of 1,3-dimethyl-1,3-dihydro-2H-IbP-2-one **226a** was investigated. The reaction proceeded in glacial acetic acid in the presence of sodium acetate; the gaseous chlorine was passed through the solution for 15 min and then the mixture was heated to yield 5,6-dichloro derivative **354a**. 5,6-Dibromo-1,3-dimethyl-IP-2-one **354b** was formed in high yield in the same medium on treating with bromine in 10% excess. It is noteworthy that monohalo derivatives of parent base **226** were not obtained regardless of reagent ratios used.

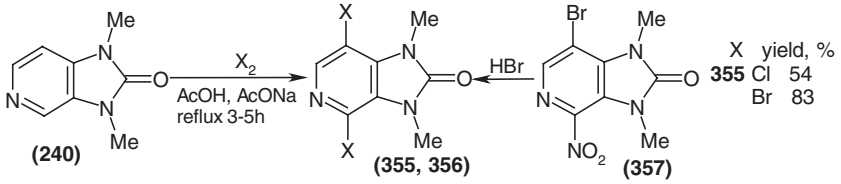
As distinct from chlorine and bromine, elemental iodine did not react with **226** under the same conditions. Only 6-iodo-1,3-dimethyl-IbP-2-one **353** formed in a reaction with iodine monochloride.

The structure of all halogenated products was proven by independent syntheses and PMR spectral data (98ZOR1420).

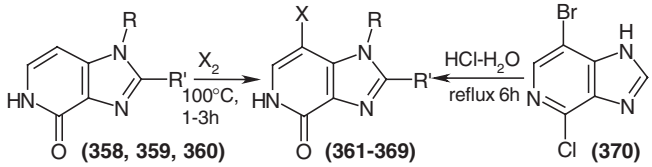


2. *Imidazo[4,5-c]pyridines*

Unsubstituted IcP and its 1- and 3-methyl derivatives are unreactive towards bromine below 160 °C, except for the formation of molecular complexes with the halogen. However, halogenation of 1,3-dimethyl-1,3-dihydro-2H-IcP-2-one **240** proceeds quite easily. Only 4,7-dichloro- or dibromo derivatives **355** of **240** are formed in acetic acid in the presence of sodium acetate. Chlorination can be carried out with gaseous chlorine or SO_2Cl_2 (94KG1076). It is worth mentioning that 4-bromo-1,3-dimethyl-IcP-2-one failed to be converted into dibromo derivative **355** when treated with bromine. The structure of dibromide **355** was proven by its identity with the product of the reaction between the 4-nitro-7-bromo-1,2-dimethyl-IcP-one **357** and hydrobromic acid where the nitro group was substituted by a bromine atom (94KG1071).

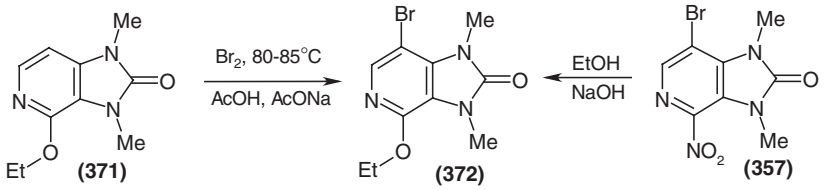


An oxo group located at both carbons 2 or 4 in IcP strongly activates the IcP. It was shown (94KG1071) that IcP-4-one **358**, and its 1- and 2-methyl analogues **359** and **360** were readily brominated under standard conditions providing 7-bromo derivatives **361**–**369,** usually in 72–88% yields. The compound **362** was also obtained by acid hydrolysis of 7-bromo-4-chloro-IcP **370**.



	X	R	R'	yield, %
361	Cl	H	H	90
362	Br	H	H	89
363	I	H	H	60
364	Cl	Me	H	42
365	Br	Me	H	88
366	I	Me	H	88
367	Cl	H	Me	70
368	Br	H	Me	72
369	I	H	Me	65

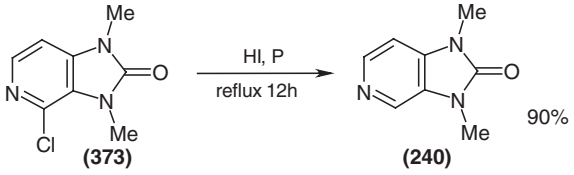
The attempted direct chlorination of compounds **358, 359** and **360** resulted in tarring. However, a reaction with sulphuryl chloride in acetic acid afforded 7-chloro derivatives **361, 364** and **367** in 4–90% yields. Iodination of the same bases occurred quite easily on treating them with iodine in aqueous alkali to form iodo derivatives **363, 366** and **369** (60–88%). Substitution occurs in the 7th position of the IcP molecule, as in the case of chlorination and bromination. In the PMR spectra of all halides **361**–**369**, only a singlet of 6-H at 7.77−7.91 ppm (in CF_3COOH) appears (94KG1076). Bromination of 4-ethoxy-1,3-dimethyl-IcP-2-one (**371**) proceeds very easily to give its 7-bromo derivative **372** in 87% yield. This compound was also obtained when nitro compound **357** was treated with ethanolic alkali (94KG1076).



The formation of chlorine-substituted IPs from oxo-IPs is described in Section V.

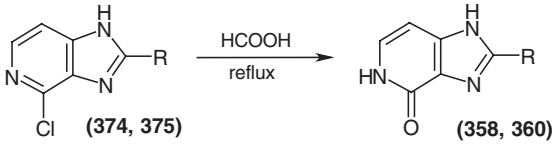
3. *Properties of Imidazopyridine Halo Derivatives*

The replacement of halogen in the IP core is the most well-known reaction of these compounds. Numerous examples of chlorine substitution in the most reactive 2,5 and 7 positions of IbP rings, as well as in 4 position of IcP rings by simple nucleophiles are published. Halogen elimination is known to take place on catalytic hydrogenation (5% Pd/C) of 6-chloro-IbP or 7-chloro-IbP (48RTC29) to afford IbP **1** in 29% yield (49JA1885), or when 4-bromo-6-amino-IcP is hydrogenated under the same conditions to give 6-amino-IcP (61%) (74JHC233). Catalytic (10% Pd/C) hydrogenation of 1- and 3-methyl-6-chloro-IcP at room temperature under atmospheric pressure results in chlorine elimination with the formation of 1- and 3-methyl-IcP in 49 and 55% yield, respectively (66JCS(B)285). Heating 2-chloro-IbP with hydroiodic acid and PH_4I for 2 h gives IbP **1** in a very low yield (57AP20). However, 4-chloro-IcP-2-one **373** refluxed with HI in the presence of red phosphorus gave product **240** resulting from chlorine elimination in high yield (94KG1071).



The acid hydrolysis of 7-chloro-5-amino-IbP was reported to afford the corresponding 7-hydroxy-5-amino-IbP in 29% yield (56JA4130) and 1,2-disubstituted 4-chloro-IcP with the same treatment afforded the corresponding 4-oxo-IcP (94JMC1632).

4-Chloro-IcP **374** and its 2-methyl analogue **375** were readily hydrolyzed when refluxed in formic acid to give the corresponding 4-oxo derivatives **358** and **360** (94KG1076). A two-stage method was used to hydrolyse 4-chloro-IcP 1-Me, 1-Bu- and 1-C_6H_{11}-derivatives. The procedure included the following steps: boiling starting substances in HCOOH and heating the residue, on removal of the solvent, for a short time with hydrochloric acid (94KG1076, 99ZOR474).



374 R = H
375 R = Me

	R	yield, %
358	H	88
360	Me	80

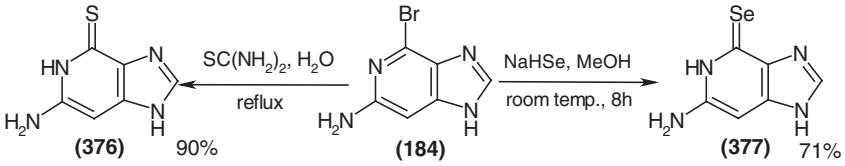
Similarly, on refluxing 1-(β-D-tri-*O*-acetylribofuranosyl)-4-chloro-IcP with acetic acid, the chlorine was replaced by an oxo group (68CPB2011). 4-Chloro-2-butyl-IcP substituted at N-3 with a bulky substituent furnished on heating with hydrochloric acid at 105 °C (40 h), the corresponding 4-oxo derivative in good yield (94JMC1632).

Chlorine atom replacement by a thione group proceeds quite readily when 4-chloro-IcP is treated with sodium hydrogen sulphide in methanol (66JMC105).

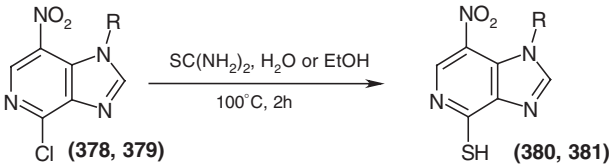
Thiourea in water or in alcohol is used for the same purpose. However, a sulphide (71RTC1166) is formed from 7-chloro-IbP.

4-Mercapto-1,3-dimethyl-IcP-2-one formation from the 4-chloride in high yield was accomplished on heating with thiourea in alcohol (94KG1071).

3-Deaza-6-thioguanine **376** was obtained analogously from 4-bromo-6-amino-IcP **184,** whereas its selenium analogue **377** was successfully prepared from bromide **184** and sodium hydrogen selenide (74JHC233).



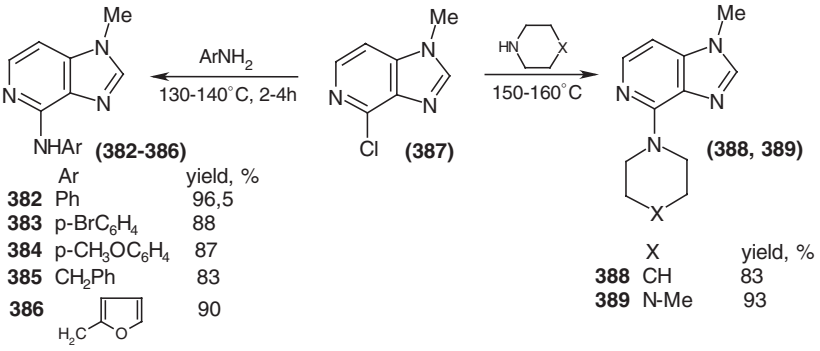
The high reactivity of 4-chloro-7-nitro-IcP **378** and its 1-methyl analogue **379** allows an easy conversion into 4-mercapto(thio) derivatives **380** and **381** in high yield on treating with thiourea (99ZOR474).



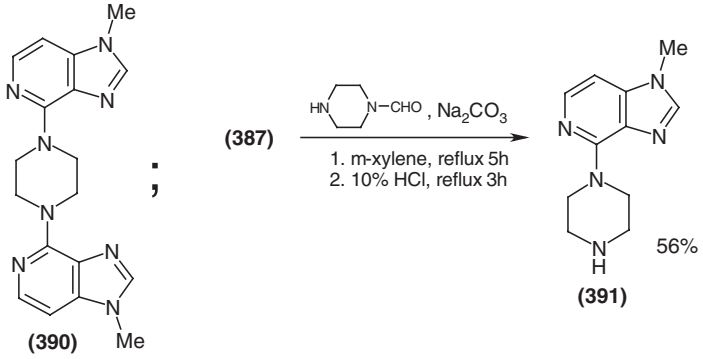
	R	yield, %
378, 380	H	89
379, 381	Me	92

The amination of 2-chloro-3-methyl-IbP **517** with 60% alcoholic ammonia at 100–110 °C gave 2-amino-3-methyl-IbP **518** in high yield. Similarly, 2-dimethylamino-3-methyl-IbP **519** was obtained (70KG1146). Chlorine replacement by an amino group in isomeric 2-chloro-1-methyl-IbP **520** proceeded with greater difficulty, affording the corresponding amine **521** (70UP1).

Transformations of 4-chloro-1-methyl-IcP **387** under the same conditions with various amines were investigated. The fusion of the chloro derivatives with anilines or benzylamines produced 4-aryl(benzyl)amines **382**–**386** in high yields. Heating **387** with cyclic amines led to the formation of the corresponding substituted **388** and **389** (96UKZ64).



Chloro derivative **387** fused with piperazine for 2 h at 150–160 °C gave a product of piperazine bisubstitution **390** in 74% maximum yield regardless of the ratio of reagents. The same **387** heated with *N*-formylpiperazine in a 1:2 ratio to the same temperature also gave bisproduct **390**. However, boiling these reagents in xylene in the presence of sodium carbonate resulted in a 70% yield of 4-(*N*-formylpiperazinyl)-1-methyl-IcP, whose hydrolysis furnished 4-piperazine-1-yl-1-methyl-IcP **391** (96UKZ64).



7-Nitro-4-chloro-IcP**,** especially its 1-methyl derivative**,** reacted with amines much more readily, affording the corresponding 7-nitro-4-amino-IcPs (99ZOR474).

The reaction of 7-nitro-4-chloro-IcP with hydrazine hydrate required heating in alcohol for 2 h, whereas the chloride reacted immediately with hydrazine hydrate after mixing in dioxane at room temperature. A similar process of the same chloride with aminoveratrole occurred within 1 h at 100–110 °C (99ZOR474).

4-Chloro-IcP unsubstituted at the imidazole N-atom, as well as 7-chloro-IbP undergo ammonolysis with difficulty even under severe conditions (170 °C, 15 h) and afford amines in low yields. These amines were obtained by hydrazinolysis of the starting chlorides followed by reduction of the intermediate hydrazine derivatives catalyzed by Raney nickel in water–alcohol solutions (49RTC1013, 69RTC1263). Replacement of a halogen atom by a hydrazine group usually proceeds very readily in the IP series. Heating 7-chloro-5-hydroxy-IbP with hydrazine hydrate is accompanied by 7-hydrazino-5-hydroxy-IbP formation in very high yield. 7-Chloro-5-amino-IbP reacts with hydrazine in the same manner. In the 5,7-dichloro derivative of IbP, the hydrazino group only replaced the chlorine atom in position 7 to afford 5-Cl-7-NH_2NH-IbP (72RTC650).

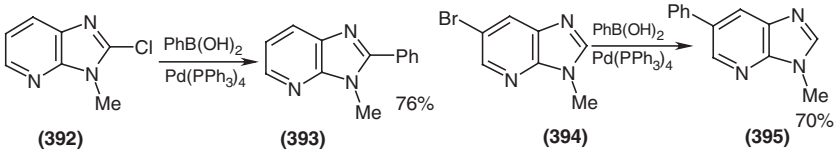
An interesting case of 5,7-dihydrazino-IbP formation from 7-chloro-5-ethoxycarbonylamino-IbP on heating with hydrazine was reported in (69RTC126).

Formation of the corresponding hydrazine derivatives from chloro IPs and subsequent transformation when heated with Raney nickel was a useful preparative synthesis of 4-amino-3-β-D-ribofuranosyl-IcP (3-deazaadenosine) (66B756), 7-amino-3-β-D-ribofuranosyl-IbP (1-deazaadenosine) (71RTC654), 4-amino-1-(deoxy-β-D-erithropentofuranosyl-1H-IcP (2′-deoxy-3-deazaadenosine) (81MI4), β-D-arabinofuranosyl-IcP (82USP4315000). The glycoside bond was preserved. ($\pm$) 3-Deazaaristeromycin (83USP4387228) was obtained in the same manner.

The chlorine atom in 7-Cl-3-ribofuranosyl-IbP glycoside can be replaced directly by methyl-, dimethyl- and furfurylamino groups at 125–135 °C (5–20 h) to give the corresponding 7-amino derivatives of N-substituted 1-deazaadenosine (71RTC654). This replacement can also be accomplished in IcP glycosides (68CPB2011). Similar replacement of a chlorine atom by the same amines was reported for 7-chloro-IbP (71RTC1166), as well as for a 7-IbP derivative (76USP3996233) by butylamine.

The chlorine atom in 4-chloro-1,3-dimethyl-IcP-2-one underwent replacement by amines (fusion with amines at 150–155 °C for 2 h) and by hydrazine (boiling with excess hydrazine hydrate for 4 h) to give the corresponding IcP amino and hydrazine derivatives. 4-Cyano-1,3-dimethyl-IcP-2-one can be obtained by boiling the 4-chloride in DMSO with KCN for 10 h (94KG1071).

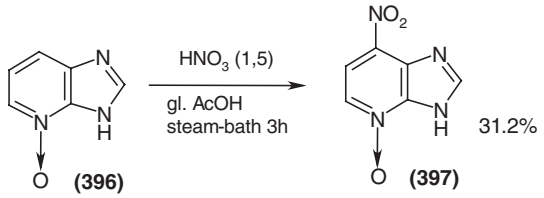
Grivas and Lindstrom developed (95JHC467) an important preparative method of introducing a C-phenyl group into the IP core by replacing a C-Hal bond. For example, the treatment of 2-chloro- or 6-bromo-IbP **392, 394** with phenylboronic acid in the presence of a catalyst (triphenylphosphine palladium complex) resulted in the respective 2- or 6-phenyl-substituted IbPs **393** and **395**.



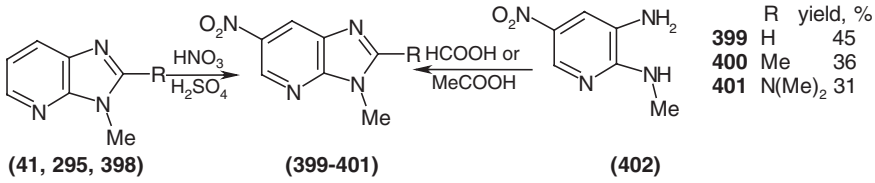
(392) **(393)** **(394)** **(395)**

K. Nitration

The direct nitration of IbP 4-oxide **396** to give 7-nitro-IbP 4-oxide **397** was the first reported example of the direct introduction of a nitro group into an IP molecule (66IJC403).



An attempt to nitrate unsubstituted IbP **1** and its 1-methyl analogue **228** failed. However, heating 3-methyl-**41** and 2-substituted-3-methyl-IbPs **295** and **398** with a nitrating mixture at 140–160 °C afforded 6-nitro-3-methyl-IbPs **399**–**401** in 45% yield. The position of the nitro group in the product was confirmed by an independent synthesis from 5-nitro-3-amino-2-methylaminopyridine **402** and formic acid (68KG953). Mild reaction conditions and the relatively high yield of nitration products, for example, of nitro compound **399**, as compared to those for pyridine nitration, reveal the great activation of the pyridine ring by the fused imidazole ring. Apparently, the nitrating agent attacks the imidazolium monocation that arises in the acidic medium (74MI1). In this cation, the pyridine ring nitrogen is shielded by the methyl group of 3-methyl-IbP **41** preventing formation of inactive dication. This assumption explains the failure of nitration in the case of unsubstituted IbP **1** and 1-methyl-IbP **228** isomer where the shielding of pyridine ring nitrogen is impossible. The above reasoning also elucidates why introducing into position 2 of 3-methyl-IbP **41** donor substituents like methyl, dimethylamino or diethylamino groups do not facilitate and even hamper nitration of the IbP core (74MI2, 74UP1).



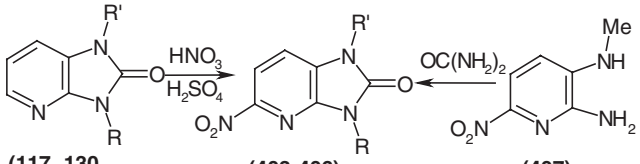
	R	yield, %
399	H	45
400	Me	36
401	$N(Me)_2$	31

Nitration of 2-amino-3-methyl-IbP proceeds at room temperature, but it is limited to the formation of a nitroamine. The attempt to rearrange this compound into a C-nitro derivative by heating with concentrated H_2SO_4 failed, as with 2- and 4-nitroaminopyridines.

An attempt to introduce a nitro group into 2-methoxy-3-methyl-IbP failed. However, it would be interesting to compare the behaviour of this compound simulating 2-oxypyridine, with the behaviour of tautomeric IbP-2-one **117** in a nitration reaction. Imidazolone **117** and its N-methyl analogues of IbP-2-one **130, 226** and **227** proved to be easily nitrated by potassium nitrate in sulphuric acid or by nitric acid

even at 0–5 °C to give mononitro derivatives **403–406** in high yields. The specific feature of this reaction is that nitro group enters the α-position of the pyridine ring to form 5-nitro-1,3-dihydro-2H-IbP and its N-methyl derivatives **403–406**.

The structure of these compounds was proved by their PMR spectra and by an independent synthesis from 6-nitro-2-amino-3-methylaminopyridine **407** (69KG378, 79UP1).

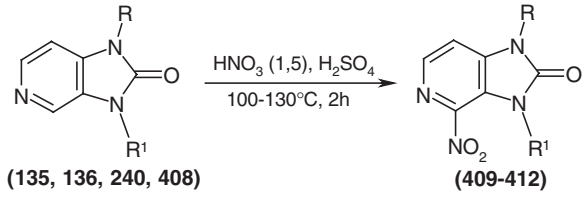


	R	R'	yield, %
403	H	H	72
404	H	Me	83
405	Me	H	76
406	Me	Me	80

As shown above, the transition from 3-methyl-IbP **41** to its 2-oxo derivative **117** and to bases **130, 226** and **227** resulted in easier nitration and a transition of the reaction site from C-6 to C-5. No other isomeric compounds were found among the nitro products **403–406**.

The IcP and its N-methyl analogues **288** and **330** are completely unreactive towards nitrating agents (86KG97). Thus, IcPs can be regarded as less reactive in electrophilic substitution as compared with isomeric IbPs. However, the introduction of a 2-oxo group into the IcP ring, as observed with IbPs, activates the compounds so strongly that the nitration becomes possible.

The reaction of 1,3-dihydro-2H-IcP-2-one **135** on nitration proceeded at about 100 °C and resulted in the formation of 4-nitro derivative **409** in high yield. 1-Methyl-IcP-2-one **136** was nitrated similarly to give **411**. However, the nitration of 3-methyl- or 1,3-dimethyl-IcP-ones **408** and **240** required more stringent conditions (up to 130 °C) (97UP1) to afford again only the 4-nitro derivatives **410** and **412**. Thus, in compounds **135**, **136**, **240** and **408**, with two vacant α-positions of the pyridine ring, only the C-4 atom suffers nitration, even in 3-methyl-IcP-2-ones **408**, where the 3-methyl group shields the reaction center (see also 2001UKZ111). Further increase in the shielding effect of an N-3-substituent, for example, as in 3-ethyl-IcP-2-one, completely prevents substitution in position 4, but this does not facilitate nitration into position 6 (73KG138, 86KG97, 94KG1071, 97UP1).

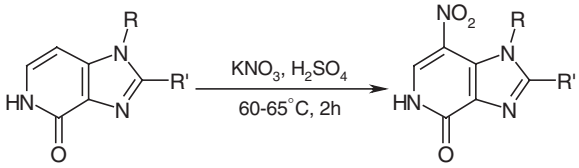


408 R = H, R^1 = Me

	R	R^1	yield, %
409	H	H	99
410	H	Me	77
411	Me	H	96
412	Me	Me	96

An oxo group in the 4 position of IcP activates even more for nitration than the oxo group in the 2 position. Even short heating of IcP-4-one **358** and its 1- and 2- substituted derivatives **359**, **360**, **413** and **414** with a nitrating mixture to 65 °C

afforded their 7-nitro derivatives **415**–**419** in high yields (99ZOR474).



413 R = n-Bu, R' = H
414 R = C_6H_{11}, R' = H

	R	R'	yield, %
415	H	H	91
416	H	Me	88
417	Me	H	67
418	n-C_4H_9	H	67
419	C_6H_{11}	H	88

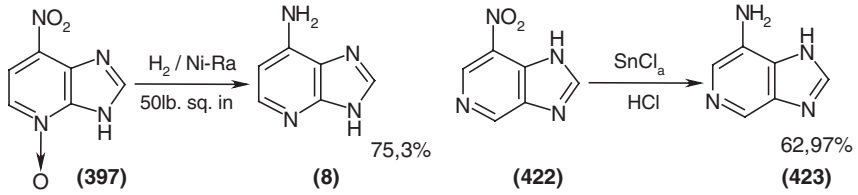
The position of nitro groups in products **415**–**417** was unambiguously proven by comparing their PMR spectra with that of nitration product **421** obtained from 2-dideuteromethyl-7-deutero-IcP-2-one **420**. Compound **420** was prepared by heating 2-methyl-IcP-4-one with deuterochloric acid (94KG1076). The PMR spectrum of deuterated **420** contained only a singlet in the aromatic region (7.20 ppm in DMSO-d_6) corresponding to a proton in position 6. This proton signal would remain or disappear depending on whether hydrogen substitution occurred on nitration at C-7 or C-6. The nitration of base **420** produced a nitro compound whose PMR spectrum contained an aromatic proton singlet at 8.32 ppm proving that the nitro group replaced the deuterium atom, i.e. was attached to C-7 atom. A similar signal was present in PMR spectra of compounds **415**–**419** (99ZOR474).

L. Reactions of Imidazopyridine Nitro Derivatives

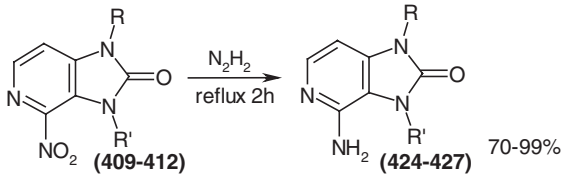
The availability of IP nitro compounds permitted investigation of their behaviour in reduction, substitution, and ring-transformation reactions.

1. *Reactions of Nitroimidazopyridines*

The principal feature of nitro compounds is their ability to be reduced into amines. Hydrogenolysis of 7-nitro-IbP 4-oxide **397** on Raney nickel afforded amine **8** with simultaneous deoxygenation of the N-oxide group (66IJC403). 7-Nitro-IcP **422** is cleanly reduced by tin(II) chloride in hydrochloric acid to give amine **423** in a good yield (57MI1, 57JA6421).

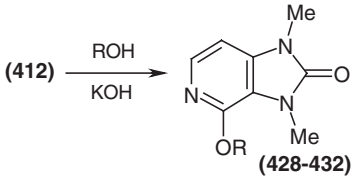


The nitro derivatives of IP-2-one are easily reduced by iron in aqueous-alcohol, by hydroiodic acid (in the presence of phosphorus), by sodium sulphide or by hydrazine affording the corresponding amines in high yields (e.g. **409–412** → **424–427**). The reduction with hydrazine occurred so readily that no metal catalyst (e.g. Ni-Raney or Pd) was required (76SUP521277, 86KG97).



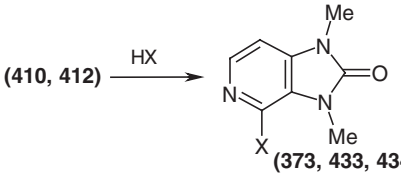
	R	R'
409, 424	H	H
410, 425	H	Me
411, 426	Me	H
412, 427	Me	Me

The nitro group in 4-nitro-1,3-dimethyl-IcP-2-one **412** was cleanly replaced by hydroxy and alkoxy groups when heated either with water or alcohols in the presence of alkali resulting in the formation of products **428–432** in a high yield (86KG97), as known to occur with 2- and 4-nitropyridine (61MI1).



	R	yield, %
428	H	80
429	Me	99,9
430	Et	95
431	n-Pr	94
432	n-Bu	85

The nucleophilic substitution of a nitro group in IPs **409–412** occurs in an acidic medium as well. These compounds when heated in HBr or HCl afford 4-chloro or bromo-IcP-2-ones **373**, **433** and **434** in high yields with the elimination of nitrogen oxide. The N-3-methyl group in compounds **410** and **412** greatly facilitates the nucleophilic replacement of a nitro group by a chlorine, fluorine or bromine atom. These compounds react with HBr, HCl or HF at an appreciable rate above 50 °C to give halides **373**, **433** and **434**, whereas unsubstituted nitro compounds react with the same acids at 150–170 °C (86KG97).



	X	yield, %
433	F	67
373	Cl	96
434	Br	87

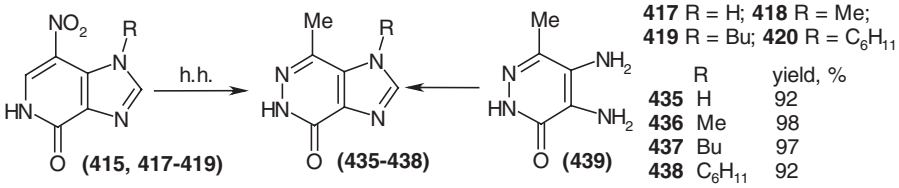
As distinct from the process with the other hydrohalic acids, 4-nitro compounds **410–412** heated in HI are reduced to 4-amino derivatives of IcP-2-one in almost

quantitative yields. The high reactivity of a nitro group in compounds **410** and **412** is in agreement with a concept of steric interaction between the 4-nitro and 3-methyl groups resulting in deviation from planarity within the molecule due to turning of the nitro group with respect to the plane of the bicycle. This leads, in turn, to decreased bond order of C-NO_2 and to higher polarization of the bond.

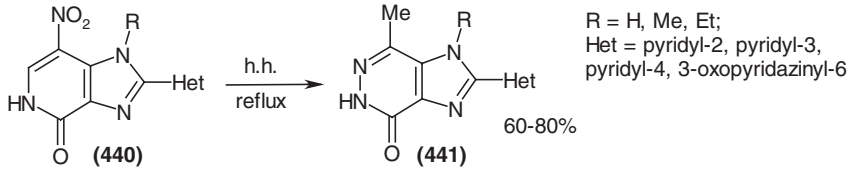
5-Nitro-1,3-dihydro-2H-IbP-2-one **403** and its N-substituted analogues **404–406**, isomeric to 4-nitro-IcP-2-ones **409–412**, do not react with HBr or HCl below 190 °C (94KG1071).

2. *Ring Transformations in 7-Nitroimidazo[4,5-c]pyridin-4-one*

An attempt to reduce nitro compound **415** with hydrogen failed because the resultant amine was immediately oxidized by air and converted into a resinous substance. However, heating this nitro compound with hydrazine afforded a stable compound that lacked both amino and hydrazine groups according to functional group analysis. Based on NMR spectra (the singlet of 2-H of the imidazole ring remained intact and the singlet of C-methyl group appeared at 2.53 ppm) and IR spectra (the carbonyl band of the cyclic amide was similar to that in the spectrum of the parent substance), it was concluded that 7-nitro-IcP-2-one **415** was transformed into 7-methylimidazo[4,5-d]pyridazine-4-one **435** (82KG705). Moreover, this compound proved to be identical to the product obtained from diamine **439** (70CPB1685). 1-Substituted 7-nitro-IcP-4-ones **417–419** (99ZOR608) were also readily converted by hydrazine into imidazopyridazinones **436–438** in high yields.

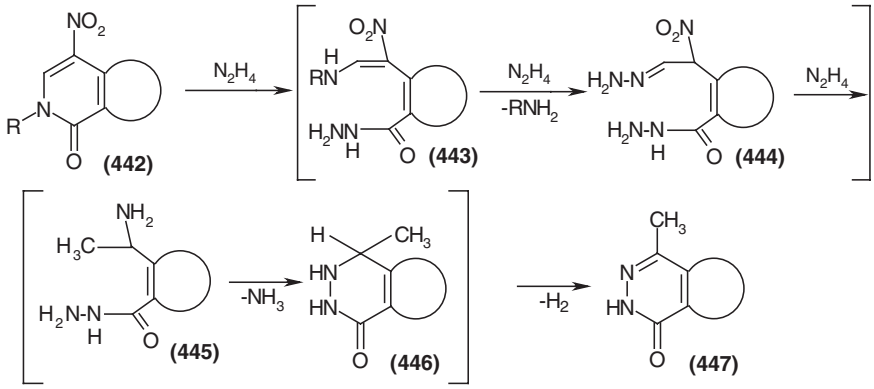


The introduction of an aryl or heterocyclic substituent in position 1 or 2 of structure **415** did not affect the type of conversion (**440**→**441**) (95MI3, 2000MI1, 2001ZOR1076).

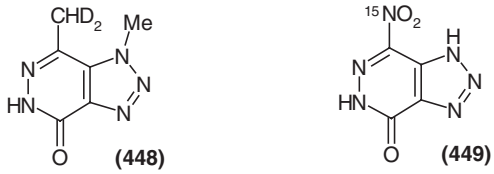


This conversion is general because it takes place in other heterocycles containing a fused 5-nitro-2-pyridone fragment such as the corresponding derivatives of triazolo[4,5-c]pyridine, isoquinoline, 1,6-naphthiridine, and thieno[3,3-c]pyridine) (86ZOR1793, 84KG132, 95ZOR304).

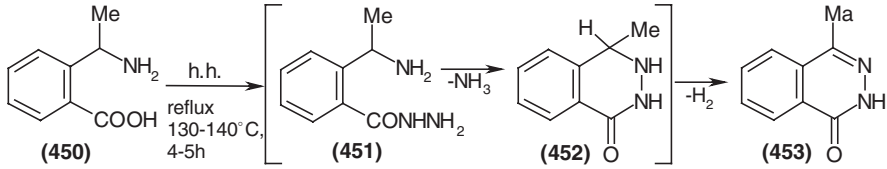
The PMR spectra of all the products of ring transformation contain signals from the new C-methyl group attached to the pyridine ring. The reaction of **447** proceeds due to the strong electron-acceptor effect of the nitro group and the carbonyl group of the pyridine fragment where nucleophilic attack of hydrazine is followed by pyridine ring opening. Hydrazine does not react with 1-methyl-IcP-4-one, its 7-bromo derivative (99ZOR608), triazolo[4,5-c]pyridine-4-one, or with 4-amino-1-isoquinoline (86ZOR1793). These observations support the assumption that the ring transformations in fused nitropyridines of general structure **442** cannot begin with nitro group reduction. The pyridine ring opening effected by hydrazine results in structure **443** that contains a carbohydrazide group and an aminonitroethylene substituent, whose transformation into a hydrazone governs the whole course of recyclization in keeping with a scheme given below (86ZOR1793). Details of the suggested mechanism of ring transformations were confirmed experimentally. It was proved that the methyl group in the structure **445** originated from hydrazone **444**.



In the PMR spectrum of the hydrazinolysis product obtained from 7-nitro-1-methyl-1,2,3-triazolo[4,5-c]pyridine-4-one in excess tetradeuterohydrazine, the signal area of the new C-methyl group is one-third of that of the N-methyl, indicating that the new group in **448** is a dideuteromethyl group (CHD_2) (99UP2). Hydrazone formation is accompanied by elimination, for example, of methylamine, as observed during the hydrazinolysis of 4-nitro-2-methylisoquinoline (84KG132). Thus, the nitrogen of the pyridine fragment is first replaced by a hydrazine group (**443** → **444**). Then the amino group from structure **445** is eliminated as ammonia following the addition of the terminal nitrogen of the hydrazide group giving **446**. In the mass spectra of hydrazinolysis products obtained from 7-NO_2(^{15}N)triazole[4,5-c]pyridin-4-one **449**, $^{15}NH_3$ was detected.

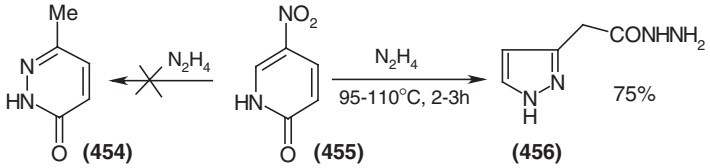


In the above pyridazine formation, both nitrogen atoms in the ring originate from hydrazine. The actual existence of intermediate structures like **445** and **446**, which are finally converted into methylpyridazinone **447**, is also supported by the fact that 2-α-aminoethylbenzoic acid **450** heated with hydrazine turns into 4-methyl-1-phthalazone **453** in almost quantitative yield through hydrazide **451** and dihydrophthalazone **452** (91ZOR1120).



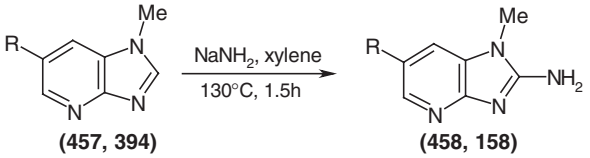
The high purity and high yield (up to 99%) of the resulting fused pyridazinones indicate that they originate from highly specific reactions. Here, pyridazine ring formation occurs with displacement of one methine group (6-CH) from the pyridine ring with its subsequent reduction into a methyl group.

This reaction is likely to be considered as a new type of ring transformation of nitrogen-containing heterocycles (99ZOR608). The necessary condition for this reaction to occur is the presence of an α-carbonyl group and a nitro group in position 5 of the pyridine ring. The third important structural element required is the presence of an aromatic ring fused to the nitropyridone. The hydrazinolysis of monocyclic 5-nitro-2-pyridone **455** did not provide the expected methylpyridazinone **454** but afforded pyrazolyl 3-acetic acid hydrazide **456** whose hydrolysis gave the acid itself (85KG1686).



M. Synthesis and Chemical Properties of Aminoimidazopyridines

Unlike *N*-alkylbenzimidazoles that are readily aminated according to the Chichibabin reaction (51ZOB884, 60ZOB590, 65MI1), 3-methyl-IbP failed to be converted into a 2-amino derivative when treated with sodium amide (70KG1146). However, the corresponding 2-amino derivatives **458** and **158** (93JOC7952) can be obtained from certain 1-methyl-IbPs **457** and **394** following the same method. The difference in 1- and 3-methyl-IbPs behaviour should be explained.



457 R = Me
394 R = Ph

	R	yield, %
458	Me	49.9
158	Ph	90.2

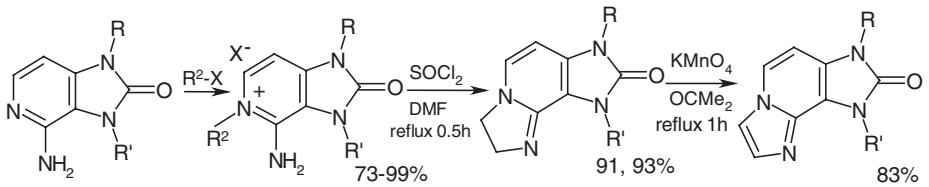
The methods of introducing an amino group onto the IP ring including reduction of nitro-IPs, interaction of chloro (or bromo)-IPs and other substituted IPs with ammonia or amines were considered in Sections IV.L.1 and IV.J.3.

In an IP molecule, the amino group has the same properties as in other amino-azaheterocycles. The character of the amino group seems to be similar to that of 2(4)-aminopyridine or even that of 3-aminopyridine. Acyl chlorides easily acylate, for example, 3-substituted 2-amino-IbP to afford an 2-acylamino derivative (77USP4059584), but 7-amino-IbP hydrochloride is acylated at the amino group and simultaneously at the imidazole ring nitrogen when refluxed with acetic anhydride for 3 h (66IJC403). 5-Amino-IbP refluxed with hexamethyldisilazane (10 h) afforded trimethylsilylation product (72%) at the amino group and at the imidazole ring nitrogen (66JPR274). 5-Amino-IbP treated with sodium nitrite in H_2SO_4 underwent a substitution of the amino group by an hydroxy group (37%) (57JA6421, 57MI1). Following the same method 5-hydroxy-7-azido-IbP was obtained from 5-amino-7-hydrazino-IbP and 5-hydroxy-7-chloro-IbP was obtained from 5-amino-7-chloro-IbP (72RTC650).

Amino group replacement by an hydroxy (oxo) group has been reported for 4-amino-β-D-arabinofuranosyl-IcP under treatment with sodium nitrite in acetic acid (82USP4315000).

Amino-IPs treated with alkali metal nitrites in hydrochloric acid give chloro derivatives (48RTC29, 65JMC708, 69RTC1263, 72RTC650). 5-Amino-2-hydroxy-IbP with sodium nitrite (0–5 °C) in 40% HF afforded 6-fluoro-2-hydroxy-IbP in 68% yield (77SUP557758). With an amino group in the β-position of the IP pyridine fragment it is possible to obtain diazonium salts whose thermal decomposition affords fluoro-containing IP (79USP4144341).

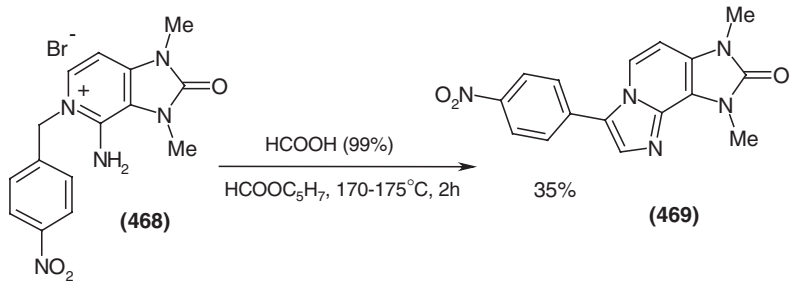
4-Amino-IcP-2-one **424** and its *N*-methyl analogues **427** are the most available 3-deazapurine derivatives (86KG97). Amines **424** and **427** react with alkyl halides to form quaternary pyridinium salts **459–463** in high yields (79MI2). Salts **459–463** heated with thionyl chloride in DMF afforded tricyclic dihydro derivatives **464** and **465**. Hydrogenation by oxidants provided substituted imidazo[4,5-c]imidazo[1,2-a]pyridines **466** and **467** (86KG227).



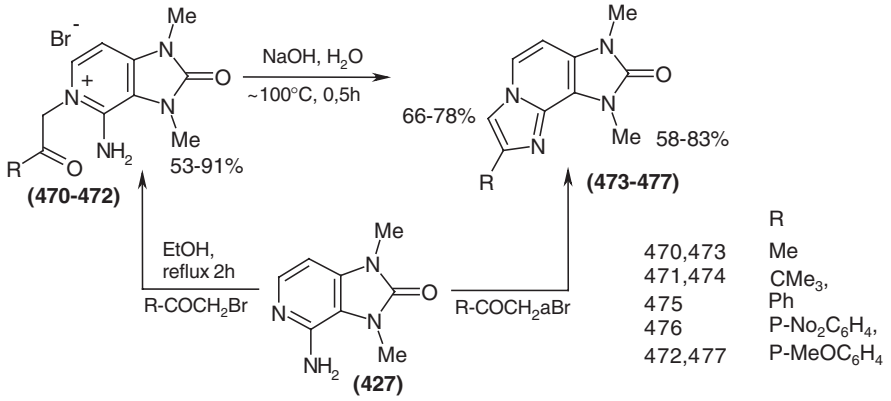
(424, 427) **(459-463)** **(464, 465)** **(466, 467)**

R = R' = H, Me;
R^2 = Me, n-$C_{12}H_{25}$, CH_2-CH=CH_2, CH_2-C_6H_4-NO_2-p, **631,632** R^2 = CH_2CH_2OH;
463, 465 R = Me; **463, 465** R' = H; **462, 464** R = R' = Me;
X = Cl, Br, I

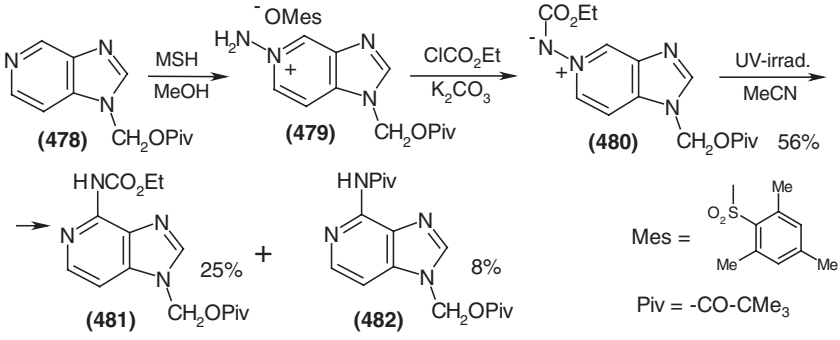
Bromide **468** heated with a mixture of formic acid and amyl formate furnished a tricycle 3-(*p*-nitrophenyl) derivative **469** (86KG227).



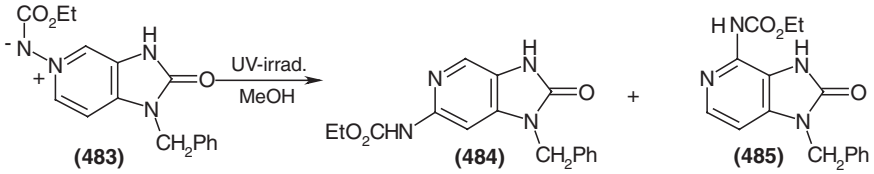
Salts **470**–**472** were obtained from amine **427** and bromoketones or bromoacetaldehyde. They were later converted into imidazo[4,5-c]imidazo[1,2-a]pyridine derivatives **473**, **474** and **477** by treatment with alkali. However, ketones like phenacyl bromide and its *p*-nitro- and *p*-methyl-substituted analogues do not give stable quaternary salts with amine **427** yielding instead tricyclic bases **475** and **476** (86KG227).



O-Mesitylenesulphonylhydroxylamine (MSH) reacts with IcP **478** to give *N*-amino-IcP **479** that converts into *N*-iminopyridinium ylide **480** when treated with ethyl chloroformate and potassium carbonate. Ultraviolet irradiation of this ylide gives a mixture of acylated amines **481** and **482** (86T1511).

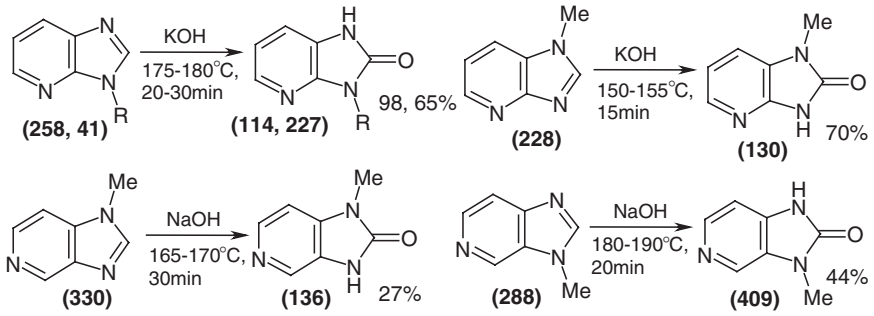


The mixture of acylated 4- and 6-amino-IcPs **484** and **485** in a 1:1 ratio in 54% overall yield was formed on UV-irradiation of IcP-2-one ylide **483**.



N. Hydroxylation

The data on hydroxylation of IPs by solid alkali are in contrast to those on the amination of 3-methyl-IbP. When compounds **258** and **41** are heated with excess potassium or sodium hydroxide up to 150–190 °C, a vigorous reaction takes place resulting in the formation of IP-2-ones **114** and **227** with elimination of hydrogen. The success of the process largely depends on the relative orientation of the imidazole and pyridine rings in compounds **41** and **288** as well as on the character of substituents at the nitrogen. Higher yields of hydroxylation products were obtained in the IbP series. The IbP **41,** the least basic compound among those under consideration, is hydroxylated at 150–155 °C to give 3-methyl-IbP-2-one **227** in almost uantitative yield. Hydroxylation of base **228** affords IbP-2-one **130** in 70% yield. This reaction turned out to be less typical with more basic IcP **288** and **330**. Here, the corresponding imidazopyridines **136** and **409** were formed in low yields. Hydroxylation of 1-benzyl-IcP failed though its "b"-isomer was reported to be readily hydroxylated to give base **114** in high yield. The behaviour of N-phenyl derivatives of IbP and IcP depends on the reaction temperature. They are either totally tarred (above 180–190 °C) or unchanged (below 160–170 °C) with the parent substance being recovered in 85–100% yield (76KG1252).

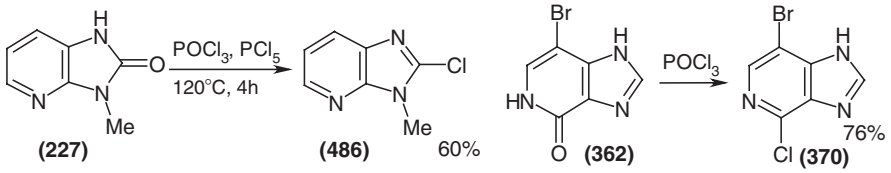


O. Properties of Oxoimidazopyridines

The simplest 2-oxo-IPs are fairly available compounds. Their high reactivity in halogenation, nitration and other (69KG378, 82KG705, 86KG97, 94KG1071, 94KG1076, 98ZOR1420) reactions make them promising starting materials for the

synthesis of more intricate deazapurine derivatives. We have already discussed oxo-IPs nitration and halogenation (Sections IV.L, IV.K, IV.M). Now we shall focus on the oxo-group reactions.

The most important reaction of oxo-IPs is with phosphorus oxychloride alone or in a mixture with PCl_5, which allows substitution of the tautomeric hydroxy group by a chlorine atom (57AP20, 64RZC887, 71GBP1114199, 70KG1146, 94H529, 94KG1076). Examples include the conversion of bases **227** and **362** into chloro IP derivatives**486** and **370**.



(227) (486) (362) (370)

Interaction of oxo-IPs with phosphorus pentasulphide is of a preparative value and leads to the formation of the corresponding thio-analogues (71RTC1166, 82USP4315000), for example, the synthesis of IcP-4-thione in 77% yield from IcP-4-one.

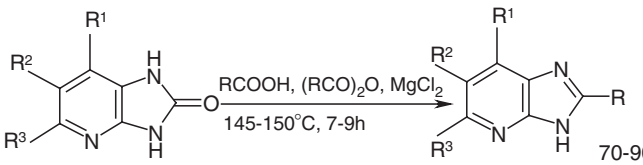
Oxo-IPs are not alkylated at the carbonyl oxygen atom by alkyl halides or diazomethane, but a reaction occurs at the nitrogen atom adjacent to the carbonyl group (68KG954). a rare and uncommon case of O-alkylation of 3-Et-IbP-2-one to give 2-*β*-diEtN-ethyloxy-3-EtIbP has been reported (70MI1). The same base was prepared from 2-Cl-3-Et-IbP.

IbP-2-one refluxed in excess acetic anhydride for 30 min afforded its diacetyl derivative of unidentified structure. Boiling the latter in water gave a monoacetyl derivative of imidazolone, whose structure also was not established (59JCS3157). But the structure of the product obtained by interaction of 6-bromo-7-methyl-IbP-2-one with acetic anhydride was claimed to be an *O*,*N*-diacetyl derivative (59JOC1455).

The reduction of 4-oxo-IcP (see Section IV.C.2) afforded the corresponding IcP dihydro derivatives, which upon treatment with iodine were readily converted into the corresponding imidazolium or pyridinium salts (78MI1).

Treatment of IcP-2-one 5-aminopyridinium salt with two equivalents of ethyl chloroformate and potassium carbonate gave an ylide of the triacylated 1,3,4-triaminopyridine (86T1511).

Senanayake et al. (94TL5775) described the conversion of IbP-2-one into IbP (e.g., **117**, **487** and **488** → **489**–**492**) upon treatment of the starting imidazolones with a mixture of carboxylic acid and its anhydride in the presence of a magnesium salt as catalyst. This reaction is of theoretical and preparative value.



(117, 487, 488) (489-492)

	R1	R2	R3	R
117, 489	H	H	H	Bu
487, 490	Me	H	Me	Et
487, 491	Me	H	Me	Bu
488, 492	Me	Me	Me	Ph

P. Reduction

The reduction of 2- and 4-oxo-IPs gives the corresponding IcP dihydro derivatives (78MI3). More detailed information on reduction of IcP and their quaternary salts will be given in the next section.

The reduction of IP nitro derivatives to give the corresponding amines was discussed in Section IV.L.1. Other substituents can also be reduced (N-allyl → N-propyl) (79USP4144341).

It is possible to deoxygenate IP N-oxides following the method applied for the simultaneous reduction of 7-nitro-IbP N-oxide during its catalytic hydrogenation. For instance, this method was used to obtain 3-ribosyl-IbP (65JOC4066) from its 4-oxide. In other cases phosphorus trichloride (reflux in $CHCl_3$) has been used to deoxygenate an N-oxide group (81UKZ867).

The reduction of hydrazine derivatives to the corresponding amino derivatives is widely used, see Section IV.J.3. Since hydrazine reacts with halo derivatives much more easily than ammonia, substrates are first converted into the corresponding hydrazine derivatives with subsequent reductive splitting with Raney nickel to give amino derivatives. Due to the mild conditions of these consecutive reactions, this synthetic approach is widely used in IP *N*-glycosides chemistry (66B756, 68CPB2011, 69RTC1263, 81MI4, 82USP4315000, 83USP4387228).

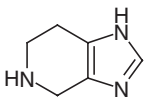
As in the case of catalytic hydrogenation of an IbP N-allyl derivative into an IbP *N*-n-propyl, the reduction of an *N*-isopropylidene substituent in 2-oxo IbP and IcP using hydrogen and palladium led to the formation of the corresponding *N*-isopropyl derivatives (69RZC573, 71JHC797).

Q. Hydrogenated Imidazo[4,5-c]pyridines

Among the known IPs only 4,5,6,7-tetrahydro-IcP (spinaceamine) and some of its substituted and more complex derivatives with an IcP ring hydrogenated to a greater extent (streptothricines) are found in plants and animals.

1. *Synthesis and Properties of 4,5,6,7-Tetrahydroimidazo[4,5-c]pyridines*

Interest in 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (spinaceamine) **493** was first due to its structural similarity to histamine **494** whose biological importance is widely known (63MI1). Spinaceamine (SpA) can be regarded as methylenehistamine. The same analogy exists between the exceedingly important amino acid L-histidine **496** and the lesser known naturally occurring amino acid spinacine (SpN) or (s)-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-c]pyridine-6-carboxylic acid **495**.



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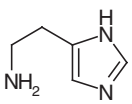

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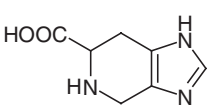

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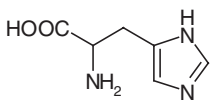
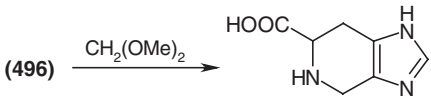


(496)

Spinacine received its colloquial name from spinach because it had been first isolated from its green leaves (24JBC303). Interestingly, the attempt to call the parent IcP "spinazol" has not been accepted (52AF515). Later, SpN was found not only in spinach, but also in crabs (*Crango vulgaris*) (41MI1), in human urine (86MI2), in shark (*Acanthia vulgaris*) liver (36MI1) and in *Panax ginseng* (87MI1). SpN is formed during cheese manufacturing when formaldehyde is added to milk as antimicrobial agent. It was shown that formaldehyde labelled with ^{14}C was bound to 99% of the terminal histidine N-residues contained in the γ-casein (88MI3, 92MI1). An HPLC method of tracing SpN in cheese is based on this fact (96MI1).

SpA was also found in animals. SpA and its 5-methyl derivative were isolated from the skin of amphibians from Southern America, Australia and Papua New Guinea (63E346, 64MI1, 64MI2, 70ZN1451, 76ZN(C)118).

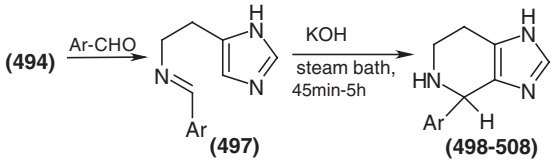
The biogenesis of SpN and SpA from histidine has been suggested (64MI1). SpN was synthesized for the first time in 75% yield before 1913 by heating L-histidine with methylal in concentrated HCl (13MI1). Later, it was obtained from histidine by treating with methylal in concentrated HCl or by treating with one equivalent of formaldehyde in water at 37 °C for two days (21MI1, 44BJ309, 91JHC97). An SpA synthesis from histamine was carried out under conditions close to physiological to afford the product up to a 90% yield (76H127). The reported methods (49MI1, 49MI2) for the synthesis of SpN were rather complicated and laborious. SpN prepared from histidine and methylal in concentrated HCl was isolated by complexing the product with silver and copper salts, and the copper complex was decomposed by hydrogen sulphide to give the amino acid in no more than 64% yield. Vitali and Bertaccini (64G296) reported on the isolation of SpN from dilute aqueous solutions; the yield of the target compound was low. Later, a simple synthesis of SpN **495** from **496** was developed that did not differ much from the previously reported one, but product isolation was simplified considerably. The mixture was evaporated to dryness, the residue was dissolved in water, and the solution was neutralized with ammonium hydrogen carbonate to obtain pure SpN **495** in no less than 75% yield (81MI2, 88KFZ20).



(495)

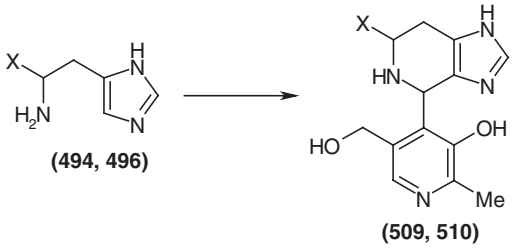
SpAs were obtained by a procedure similar to the SpN preparation (21MI1, 63E346, 64G296, 65FES634, 67FES821, 76H127, 81JA6338, 94JHC453). SpNs and SpAs with substituents in position 4 are obtained when instead of formaldehyde aliphatic or aromatic aldehydes are applied. The reaction occurs smoothly in the presence of alkali in aqueous alcohol with equivalent amounts of reagents. Schiff base **497** first forms and that is cyclized into SpA under heating. Schiff base **497**

formed exothermal and in quantitative yield also affords SpAs **498**–**508** on heating (66JOC2380, 67FES821).



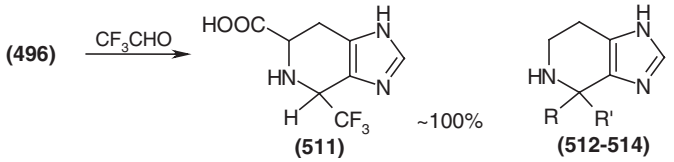
498 Ar = Ph
499 Ar = 4-MeOPh
500 Ar = 4-ClPh
501 Ar = 2-ClPh
502 Ar = 3-NO_2Ph
503 Ar = 3-FPh
504 Ar = 4-FPh
505 Ar = 4-Py
506 Ar = 3,4-(OCH_2O)Ph
507 Ar = furyl-2
508 Ar = thienyl-2

Histamine and histidines (**494**, **496**) react with pyridoxal to give SpAs with interesting structures **509** and **510** containing also a fragment of vitamin B_6 (48JA3429, 48JA3669, 67FES821, 81JA6338). Here also Shiff bases are intermediates.



509 X = H, 29%
510 X = COOH

Condensation of histidine **496** with trifluoroacetaldehyde proceeds with the formation of 4-trifluoromethyl-SpN **511** (87JFC581, 94JHC453).

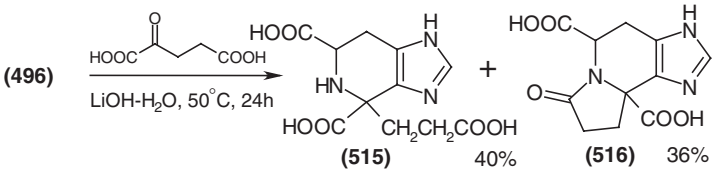


512 R = R' = Me,
513 R = R' = $(CH_2)_4$,
514 $(CH_2)_5$

Ketones react similarly as aldehydes to give disubstituted SpNs and SpA, for example **512**–**514** (67FES821).

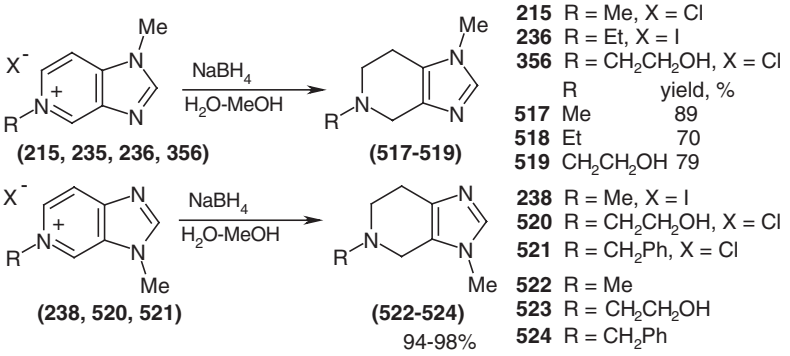
Pathogenic soil bacteria *Agrobacterium tumifaciens* and *Agrobacterium rhizogenes* induce tumour growth in dicotyledon plant roots, resulting in changes in the metabolism of these plants and in the production of cucumopin **515**, which turned

out to be an SpN derivative. The latter, as well as its lactam **516,** is formed when L-histidine is slightly heated with α-ketoglutaric acid in aqueous alkaline (pH 12.5) (88H2423).

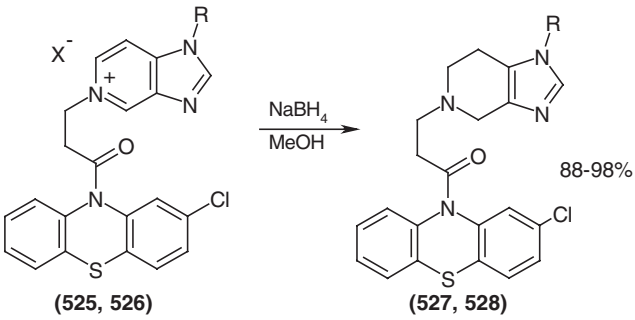


The above methods of SpN and SpA synthesis were based on the Pictet–Spengler reaction, which in some cases was used with great success. However, among the 4-*β*-aminoethylimidazoles required for this reaction, only histidine and histamine are available, the latter being less accessible. Therefore the preparation of N- and C-substituted SpAs (SpNs) by a Pictet–Spengler reaction is hardly probable.

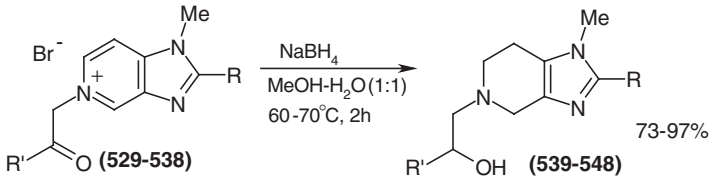
An SpA synthesis based upon a reduction with sodium borohydride of 1- and 3-substituted IcP quaternized at N-5 atom is very promising. As shown by Yutilov et al., this reaction proceeds smoothly in aqueous methanol at room temperature and affords N-1, N-5 and N-3, N-5 disubstituted derivatives of SpAs **517**–**519** and **522**–**524** in almost quantitative yields (81KG992, 89KFZ56). In the UV region, these bases, as distinct from the parent salts, absorb only at 206 nm ($\log \varepsilon \approx 3.7$–$4.10$) like imidazoles and SpNs prepared from histamine (81KG992). A comparison of the PMR spectra of the parent aromatic salts **215**, **235**, **236**, **238**, **356**, **520** and **521** with those of reduced products **517**–**519** and **522**–**524** revealed that signals of the aromatic pyridine protons disappeared, but the imidazole signals were still present (for nitrogen or C-2 substituents), and signals of aliphatic protons at positions 4, 6 and 7 of the bicycle appeared (89KFZ56).



The reduction of IcP 5-*N*-(*β*-chloropropionyl)-2-chlorophenothiazine chloride **525** and **526** under the same conditions gave phenothiazine derivatives of SpA **527** and **528**, which are of pharmacological interest (98MI2, 2001KFZ16).

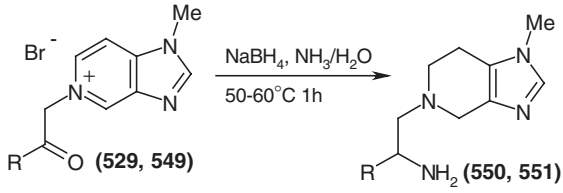


5-Acylmethyl salts of IcP **529**–**538** were reduced by sodium borohydride in aqueous methanol to SpNs **539**–**548** with a 5-(*β*-substituted *β*-oxyethyl) substituent. The carbonyl group was also reduced (IR spectra) (89KFZ56, 89KFZ160).



	R	R'
529, 539	H	CMe_3
530, 540	H	4-BrPh
531, 541	H	3,4-$(MeO)_2$Ph
532, 542	Me	4-(MeO)Ph
533, 543	SMe	Ph
534, 544	SMe	4-(MeO)Ph
535, 545	3,4,5-$(MeO)_3$Ph	CMe_3
536, 546	3,4,5-$(MeO)_3$Ph	4-BrPh
537, 547	3,4,5-$(MeO)_3$Ph	Ph
538, 548	3,4-$(MeO)_2$Ph	Ph

When the same 5-acylmethyl salts, for example, **529** and **549**, were subjected to borohydride reduction in a concentrated aqueous ammonia solution, reductive amination of the carbonyl group took place to afford compounds **550** and **551** (2001UKZ111). Simultaneously, the pyridine ring was exhaustively hydrogenated.

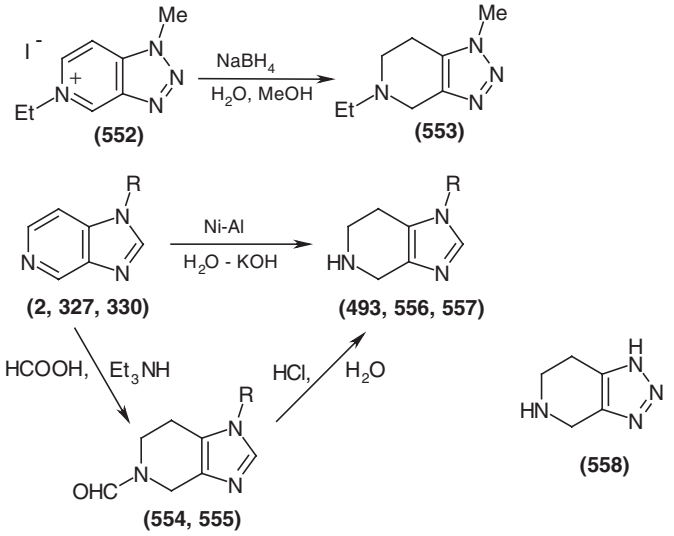


549 R = n-(MeO)Ph

	R	yield, %
550	CMe_3	93
551	n-(MeO)Ph	69

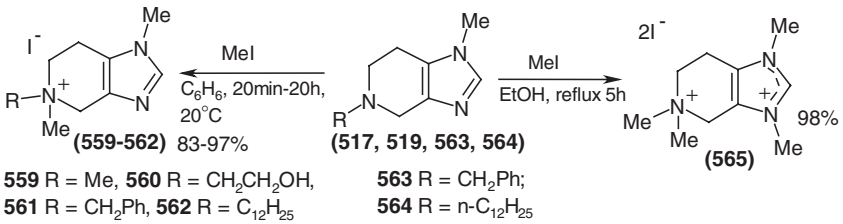
The reduction of quaternary salts of 2-aza-IcP, i.e. triazolo[4,5-c]pyridine, for example **552**, by sodium borohydride gives 2-aza-SpA derivative **553** (94ZOR440, 94KFZ58).

A more universal method of SpAs preparation is based on reduction of IcP bases (e.g., **2**, **327** and **330)** instead of the IcP quaternary salts mentioned above. The reduction was performed with nickel aluminium alloy or, better still, with a mixture of formic acid and triethylamine. In the latter case, reaction results in the formation of isolable 5-formyl SpAs derivatives (e.g., **554** and **555)** readily hydrolyzed in hot hydrochloric acid to SpAs in 85–95% yield, unsubstituted (**493**) or substituted (**556** and **557**) at the ring nitrogen atoms. By this method, the previously unknown 2-aza-SpA **558** were prepared from 1,2,3-triazolo[4,5-c]pyridine (2002ZOR440).

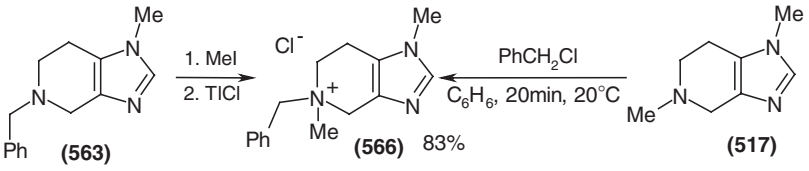


Crystallographic and X-ray data of spinacine were reported in (64RS718) and (71G625).

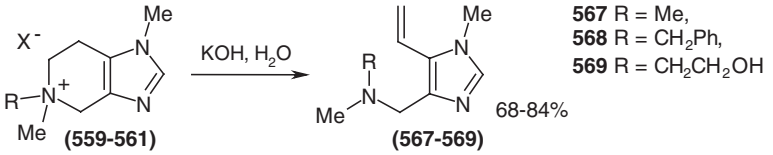
Spinaceamines are fairly strong bases with two basic centres. The highest protonation constants correspond to the N-5 atom of SpA (8.90) and the N-5 atom of SpN (8.66), while the smaller constants characterize the basicity of the imidazole ring in the monocation of SpA (4.89) and SpN (4.96). The acid ionization constant of SpN (pK_a) is 1.65 and is comparable with the pK_a of histidine (1.96) (73JCS(D)323). SpNs **517**, **519**, **563** and **564** substituted at an N-atom easily take up methyl halides to afford monoquaternary salts **559**–**562** at the N-5 atom. More stringent conditions are required to obtain diquaternary salts **565** (82MI5).



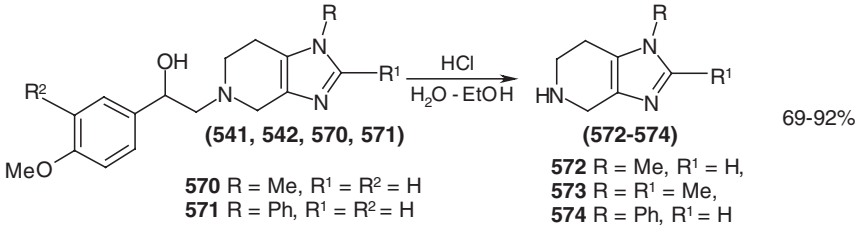
The mixed alkylation of 5-benzyl-1-methyl-SpA **563** and 1,5-dimethyl-SpA **517** was carried out to prove the structure of SpA monoquaternary salts. When **517** was treated with benzyl chloride and base **563** was treated in succession with methyl iodide and an aqueous solution of thallium(I) chloride, the product was the same 5-benzyl-1,5-dimethyl SpA chloride **566** from both (82MI5).



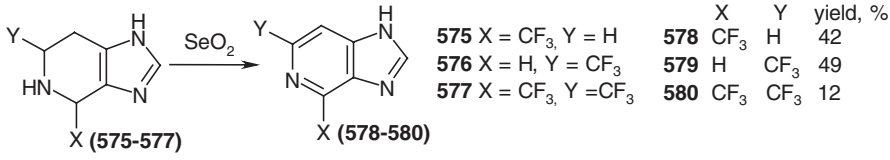
Salts **559–561** treated with alkali underwent ring-opening to 5-vinyl-4 amino-methyl-1-methylimidazole derivatives **567–569** (82MI5).



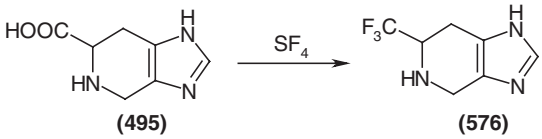
An interesting property was discovered for 5-(*β*-oxy-*β*-phenethyl-*H*-SpA)s containing a 4-methoxy group or 3,4-dimethoxy groups in the phenyl ring **541**, **542**, **570** and **571**. On heating in hydrochloric acid, the molecule cleaved at the terminal C-N bond providing SpAs **572–574** unsubstituted at N-5 (83KG1134). Similarly, 2-aza-SpA derivatives were cleaved in the same fashion (94ZOR440).



The oxidation of SpAs to afford IcP, a reverse reaction with respect to IcP reduction, is less typical. The oxidation of SpNs with selenium(IV) oxide in acetic acid gave IcPs (82H1003). More definite data were reported on the oxidation of fluoro-substituted SpNs and SpAs **575–577** into IcPs **578–580** (94JHC453).

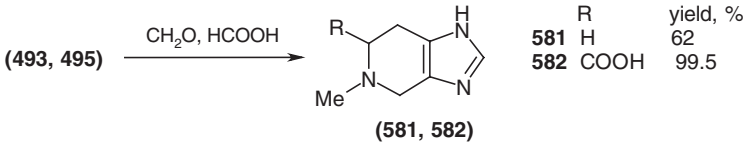


Compound **576**, prepared from SpN **495** on treatment with SF_4, was similarly oxidized (94JHC453).

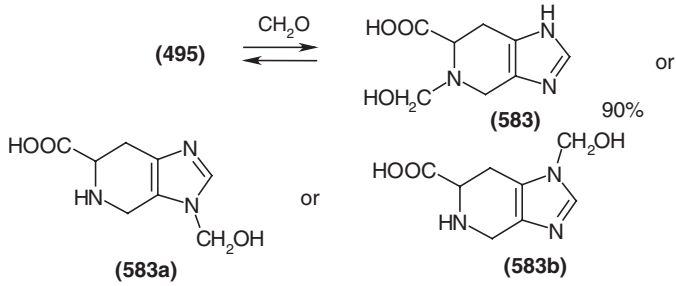


Thermal decarboxylation of SpN **495** into SpN **493** proceeded with difficulty as commonly found for other α-aminoacids, i.e., at a high temperature, and afforded product in low yield (44BJ309).

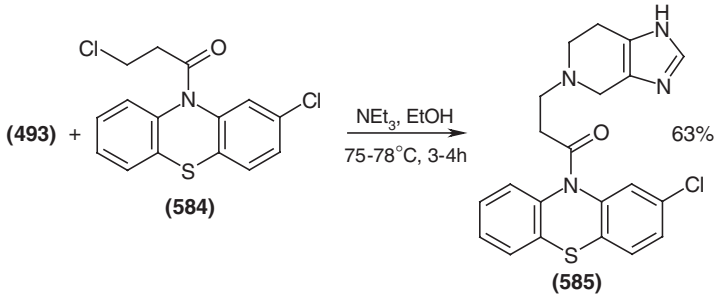
SpA **493** and SpN **495** are easily methylated with formaldehyde and formic acid, an Eschweiler–Clarke reaction, to give 5-methyl derivatives **581** and **582** (63E346, 88KFZ20, 64G296, 91JHC97).



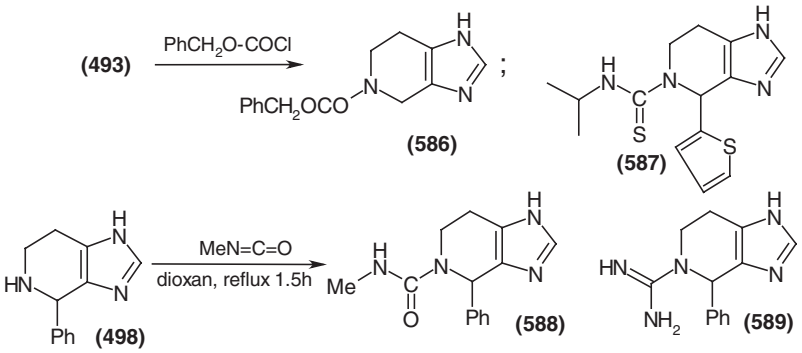
SpN readily takes up only one mole of formaldehyde in aqueous solution to give an N-oxymethyl derivative with an unidentified structure, possibly **583** or **583a,b**. When this derivative is either heated or acidified, one mole of formaldehyde is liberated (44BJ309).



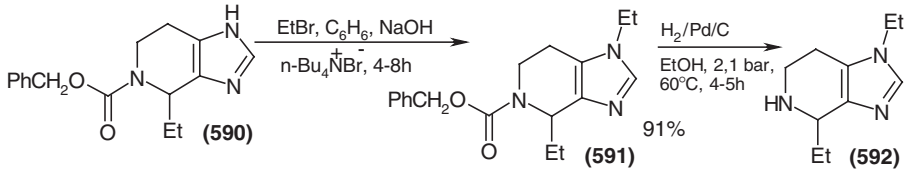
Alkylation of SpA with *N*-(*β*-chloropropionyl)-3-chlorophenothiazine **584** led to the formation of **585** with a structure similar to that of Nonachlazin, used in cardiac ischemia treatment (98MI2, 2001KFZ16).



SpAs, for example **493** and **498**, are readily acylated with acyl chlorides, isothiocyanates, isocyanates, and isourea salts to form the corresponding N-5 substituted derivatives **586–589** (79SUP667136, 80SUP791241).

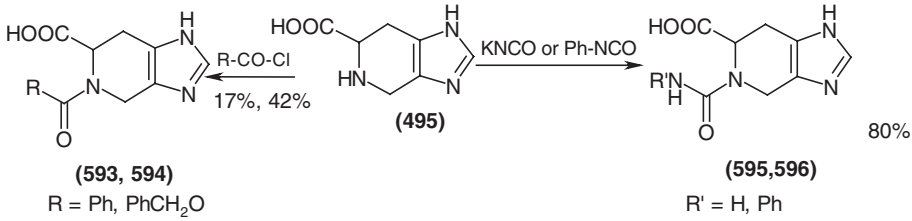


Acylated SpAs (e.g. **590**) can be alkylated at an imidazole ring nitrogen to form a mixture of 1- and 3-alkyl isomers, the 1-alkyl isomers **590** prevailing (80SUP791241). Hydrogenation of **591** gives 1- (**592**) and 3-alkyl-5H-SpAs.

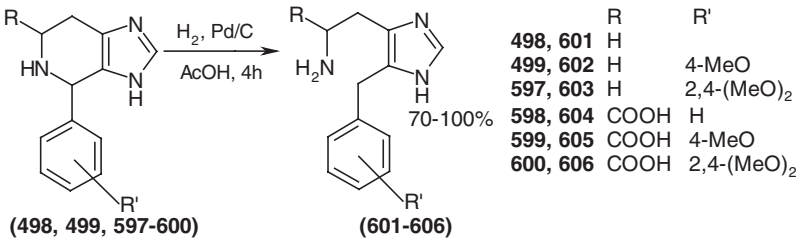


SpN **495** was also acylated by acid anhydride, benzoyl chloride, benzyl chloroformate, potassium cyanate, and phenyl isocyanate to give **593–596** (91JHC97).

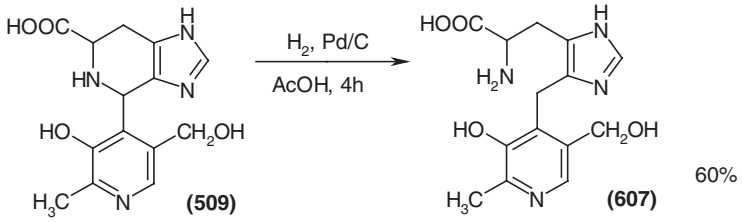
A benzoylated diaminotetrahydropyridine (44BJ309) was obtained when SpA **493** was treated with benzoyl chloride in the presence of an alkaline solution.



Emmett et al. hydrogenated 4-phenyl-SpA **498** with a palladium catalyst for 26 h under high hydrogen pressure to obtain 5-benzylhistamine **601** in 79% yield (82JMC1168). Yutilov et al. recently found that this reaction readily proceeded under atmospheric pressure at room temperature to give the same product **601** in a quantitative yield. Similarly, from substituted 4-phenyl-SpAs **499** and **597–600** benzylhistamines **602** and **603** and benzylhistidines **604–606** substituted in the phenyl ring were obtained (95JOU1429, 95ZOR1577, 2001ZOR129).



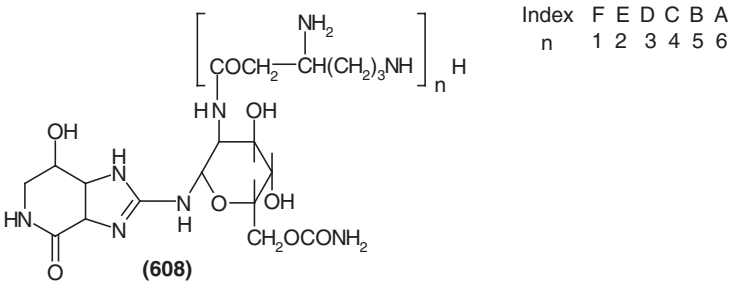
A hybrid of vitamin B_6 and histidine was obtained in the same way (**509** → **607**) (95ZOR1577, 2001ZOR129).



2. *Streptothricines*

Some strains of *Streptomyces* are able to produce a series of antibiotics of similar activity; they are designated streptothricines (StTs) (54JA566). Six substances with a similar behaviour were separated from different antibiotics of streptothricine group and were indexed as A-Fourth varying repeating units. The structure and properties of these antibiotics were extensively studied.

Based on an investigation of the hydrolysis products of StTs, van Tamelen, Carter et al. derived structural **608** where the principal fragment was a hydrogenated IcP derivative bonded to either an L-β-lysine amino acid or an α-D-glucosamine amino sugar or sometimes a D-glucosamine (61JA4296, 63MI3, 65KPS42, 65KPS117, 72DOK1119).

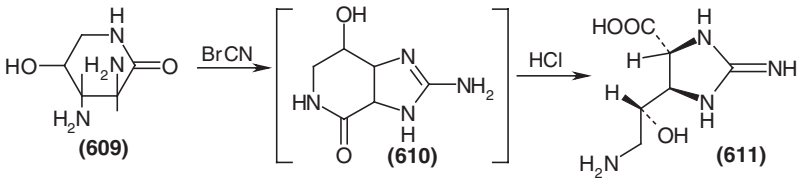


Under known conditions for the biosynthesis of StT and in the presence of 2-aminoadipic acid, Voronina et al. succeeded in preparing a new antibiotic,

streptothricine-X, containing seven β-lysine groups (69MI4, 72DOK1119). Fucothricine containing another amino sugar, fucosamine, was assigned to antibiotics of the streptothricine group (71MI2).

Antibiotics of the streptothricine group are unstable in acid and especially in alkali. Their salts with mineral acids are insoluble in organic solvents, their IR spectra are identical, and the melting points of their salts are very similar (65KPS42).

In 1974, Goto and Ohgi prepared streptolidine **611** by a reaction of bromocyane with arabinose triamino-γ-lactone followed by hydrolysis of intermediate **610** with hydrochloric acid (74TL1413). Kusumoto et al. at the same time reported the synthesis of streptolidine lactam **610**, prepared in turn from 3,4-diamino-5-oxopiperidone-2 **609**. Although the latter compound was not identified, its hydrolysis under reflux in 6 N hydrochloric acid led to the formation of streptolidine **611** (74TL1417).



Carter et al. were the first to derive the correct structure of streptolidine (61JA4296), and Bycroft and King have determined its exact molecular configuration by X-ray analysis (72JCS(CC)652).

R. Oxidation

Reactions described here are common to the other heterocycles of this type and are diverse. These are N-oxidation, oxidation of C-methyl groups and thiol substituents in IPs and their dihydro derivatives. Importantly, the most available 2-methyl- and 2-mercapto-substituted IPs can be so converted.

1. *N-Oxidation of Imidazopyridines*

Formation of N-oxides is the simplest IP conversion except for protonation. N-oxidation usually was done by the Ochiai procedure (53JOC534), namely with hydrogen peroxide or peracids. In IbP and IcP, the pyridine nitrogen is always N-oxidized, for example, **1** → **396** (49JA1885, 59JOC1455, 64JOC2611, 65JOC4066, 66IJC403, 80JHC1757, 83BRP2113675, 91TL6915, 94MI2).

IP N-oxides are valuable intermediates for introducing nitro, hydroxy, halo, and cyano substituents into the parent substances (66IJC403, 78H113, 80JHC1757, 82JHC513).

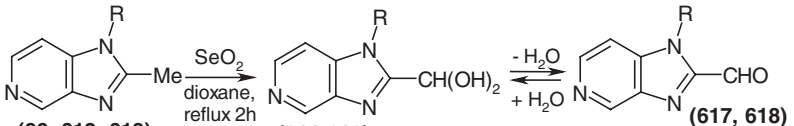
2. *Oxidation of Methylimidazopyridines*

Oxidation of C-methyl derivatives of IPs is a very important reaction for the preparation of aldehydes, carboxylic acids, thioamides and other derivatives. The

formation of carboxy-IPs by treating methyl-IPs with potassium permanganate occurred with mixed success as was also observed for other aromatic series (59JOC1455, 67SUP207143, 69JHC759).

2-Styryl-IcP formed by condensation of 2-methyl-IcPs with benzaldehyde afforded 2-carboxy-IcP when oxidized with potassium permanganate.

Selenium(IV) oxide, a milder oxidizing agent compared to potassium permanganate, oxidized 2-methyl-IPs **86**, **612**, **613** to 2-formyl-IPs **614–616** in high yields.



(86, 612, 613)
613 R = CH_2Ph

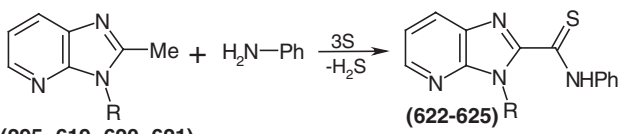
(614-616)

	R	yield, %
614	Me	75
615	CH_2Ph	84
616	Ph	50

(617, 618)
617 R = Me
618 R = CH_2Ph

Aldehydes of the "c"-series **617** and **618** easily add water providing monohydrates **614–616** stable at room temperature. No carbonyl absorption band appeared in the IR spectra of these monohydrates (KBr pellets). The absorption in the 1705–1720 cm^{-1} region appeared in CCl_4 solution only when the sample had been dried *in vacuo* at 105–110 °C (5–10 mmHg, 2 h). These facts show that aldehydes **617** and **618** undergo covalent hydration of the carbonyl group forming a gem-dioxymethyl group. Aldehydes of "b" series do not form hydrates and possess strong carbonyl absorption bands in their IR spectra in the 1700–1710 cm^{-1} region. All the above-mentioned aldehydes behave identically in chemical reactions providing oximes, hydrazones, and take part in condensations (75KG1389).

2-Methyl-IPs are readily oxidized by elemental sulphur by the Wilgerodt–Kindler reaction. Yutilov and Shcherbina found that compounds **295**, **619**, **620** and **621** were cleanly oxidized with sulphur in the presence of aromatic amines at 170–180 °C to give IP 2-thiocarbanilides **622–625**. At a ratio of 2-methyl-IP–sulphur–amine of 1:5:4, the reaction was complete in 15–20 h, and the yields of the resulting thioanilides were 60–81%. IbP **623** and **624** were obtained in quantitative yield at an equimolar ratio of the substrate and sulphur and double excess of aniline (96ZOR586, 96JOU564).



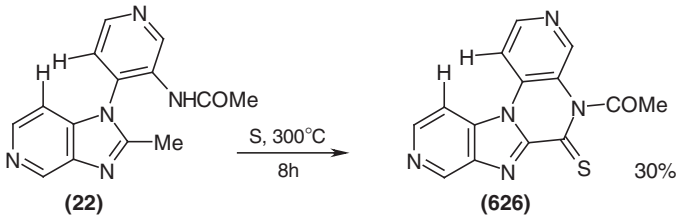
(295, 619, 620, 621)
621 R = H

(622-625)

	R	yield, %
622	H	72
623	Me	99
624	CH_2Ph	99
625	Ph	60

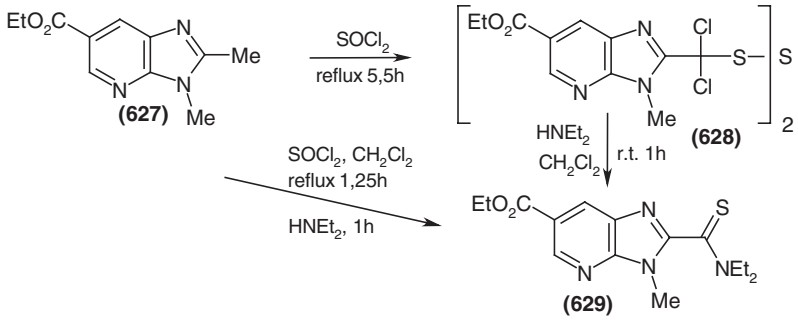
An intramolecular Wilgerodt–Kindler reaction is performed by fusion of IcP **22** with sulphur at 300 °C to form tetracyclic base **626** in low yield. Presumably, this

cyclization requires severe conditions due to the steric repulsion of the hydrogen atoms in structures **22** and **626** that hampers a planar arrangement of the rings and hinders the formation of a new ring (96ZOR586, 96JOU564).



(22) (626)

It is interesting to compare the product of the interaction of 2-methyl-IbP **627** and excess thionyl chloride with that from a Wilgerodt–Kindler reaction. Short refluxing of this mixture gave a trisulphane of unusual structure **628** in low yield that at room temperature with diethylamine for a short time resulted in its conversion to 2-carbothioamide **629**. The treatment of 2-methyl-IbP **627** with thionyl chloride in dichloromethane and then by amine furnished 2-carbothioamide **629** (89JHC1819).

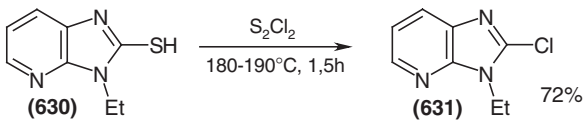


(627) (628) (629)

3. *Oxidation of Imidazopyridine-2-thiones*

The easy preparation of IP 2-thiones (thiols) makes them the most available IP derivatives and therefore their further conversions are obviously very important.

The oxidation of 3-ethyl-IbP 2-thione **630** by sulphur monochloride under severe conditions leads to a replacement of the thiol group by a chlorine atom to afford 2-chloro-3-ethyl-IbP **631** (70MI1).

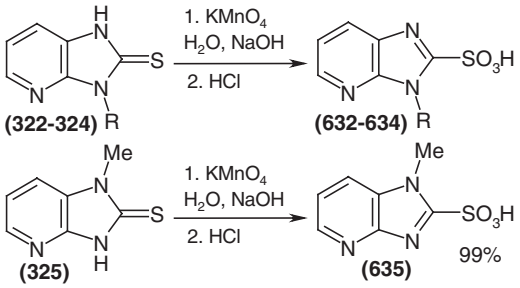


(630) (631)

Compounds like 2-benzylthio-IbP can be easily oxidized by *m*-chloroperbenzoic acid at low temperatures to give the corresponding sulphoxides (92FES287).

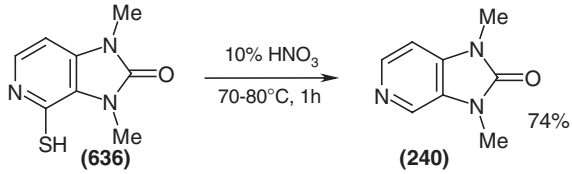
S-Benzylthio-IcP of similar structure was oxidized by a mixture of Perhydrol and selenium(IV) oxide in aqueous methanol to afford sulphoxide (92USP5081253).

IP 2-thiones **322**–**324** and **325** were oxidized by potassium permanganate in aqueous alkali to very pure samples of IP 2-sulphoacids **632**–**634** and **635**, respectively, in high yields (89UP1).

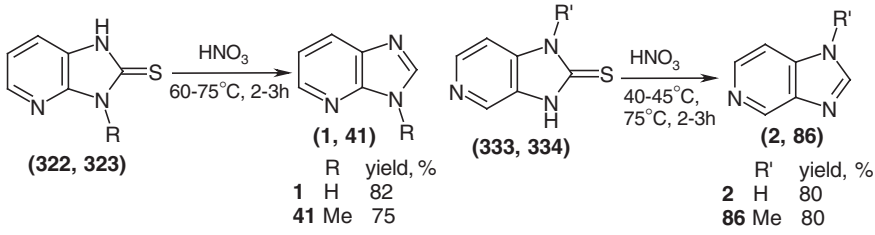


	R	yield, %
632	H	99
633	Me	87
634	CH_2Ph	92

Interaction of 4-mercapto-IcP-2-one **636** with dilute nitric acid on short heating gave a good yield of IcP-2-one **240** unsubstituted in position 4 (94KG1071).



Elimination of sulphur occurred when IP 2-thiones **322**, **323**, **333** and **334** were heated with 5–10% nitric acid resulting in the formation of the corresponding IPs unsubstituted in position 2 (**1**, **2**, **86**, and **41**) (71KG428). This simple procedure is a useful preparative method for the latter compounds.

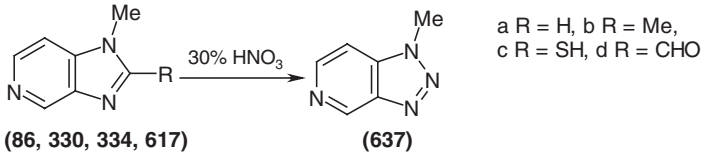


	R	yield, %
1	H	82
41	Me	75

	R'	yield, %
2	H	80
86	Me	80

However, heating thione **334** with 30% nitric acid results in the unexpected formation of a product originating from a ring transformation of the parent substance, 1-methyltriazolo[4,5-c]pyridine **637,** in 15% yield. The usual desulphurization

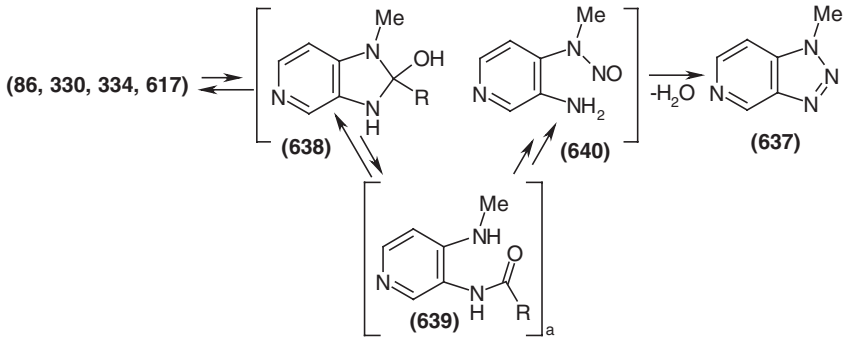
product, 1-methyl-IcP **86**, was also isolated. It is worth mentioning that triazole **637** was also obtained in a low yield from 1-methyl-IcP **86**, 1,2-dimethyl-IcP **330** and 2-formyl-1-methyl-IcP **617** on heating with dilute nitric acid (80KG121).



(86, 330, 334, 617) **(637)**

These facts suggest that the imidazole ring in compounds **86**, **330**, **334** and **617** is first reversibly covalently hydrated in the acid medium to form **638**, and then a hydrolytic ring opening occurs to provide intermediate **639**. Then *N*-nitroso compound **640** forms and ring closes to afford 1-methyl-1,2,3-triazolo[4,5-c]pyridine **637** (80KG121). The *N*-nitrosation occurs with nitrogen oxides formed from nitric acid reduction.

To simplify the scheme we represent all participants in the unprotonated form, though *N*-protonation plays a significant role in the process, especially at the stage of covalent hydration of imidazole cycle in structures **86**, **330**, **334** and **617**.

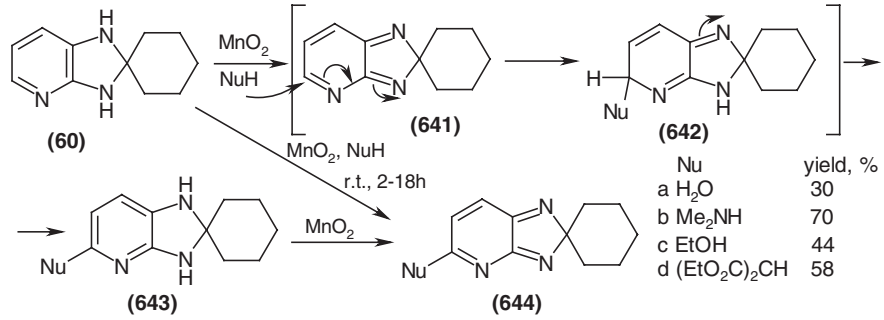


4. *Oxidation of Imidazopyridine Quaternary Salts and Dihydro Derivatives*

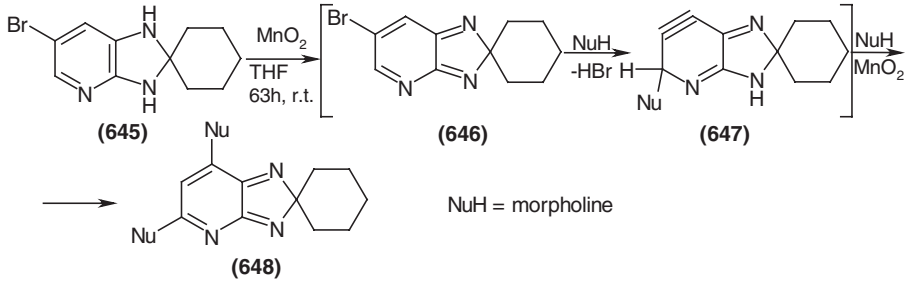
IP's oxidation processes directly affecting the imidazole and pyridine rings were seldom observed. But oxidation of 1,3-dimethyl-IbP iodide and other salts of a similar structure by potassium ferrocyanide in alkaline medium at temperatures below 10 °C afforded 1,3-disubstituted IbP-2-one (68KG954) (Section IV.C.1).

The oxidation of IcP dihydro derivatives was considered in Section IV.C.2. The oxidation of dihydrospirocyclohexane-IPs presents a more interesting case.

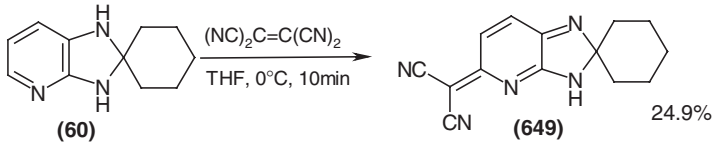
Bussolotti et al. (91TL6503) found that on treating 1,3-dihydro-4-azabenzimidazol-2-spirocyclohexane (dihydro-IbP) **60** with manganese(IV) oxide in the presence of a nucleophile, the oxidation of the main structure occurs simultaneously with an attack on the C-5 atom by the nucleophile to give substituted compounds **643** and **644** through intermediates **641** and **642**.



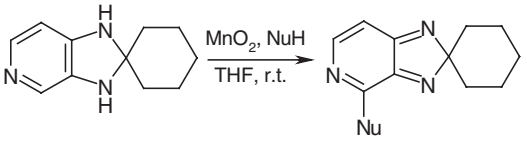
Spiro[cyclohexane-1,2′-(3′H)-1*H*-imidazo[4,5-b]pyridine] 5-bromo derivative **645** reacts similarly with manganese(IV) oxide in the presence of a nucleophile. The oxidation of this substance led to the formation of intermediate **646** which perhaps then underwent dehydrobromination in the presence of morpholine and gave intermediate dehydropyridine **647** with a 6,7-triple bond in the ring. The final base **648** formed as a result of addition of the second nucleophilic molecule across the 6,7-triple bond (94HCA2175).



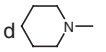
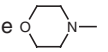
The 5-dicyanomethylene derivative of spiro[cyclohexane-1,2′-(5′H)-3′*H*-imidazo-[4,5-b]-pyridine]-5′-ylidene **649** was prepared from base **55** by treating with tetracyanoethylene at low temperature. In this case tetracyanoethylene acted both as an oxidizing agent and a reagent.



Dihydrospirocyclohexane-IcP **650** also reacted with manganese(IV) oxide and nucleophiles to give 4-substituted derivatives of the parent base **651** (94HCA2175).



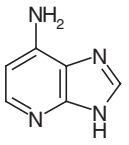
(650) (651)

Nu	time, h	yield, %
a Et_2N	1	29
b PrNH	1	50
c MeO	20	25
d 	1	60
e 	1	65

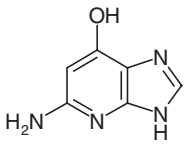
V. Biological Activity of Imidazopyridines

The IP derivatives are known to possess versatile biological activity. There are derivatives that demonstrate antiviral, cytostatic, antimicrobial, fungicidal, cardiovascular, antisecretory and other functions. However, it is possible to distinguish three classes of compounds among the IPs. These classes are believed to be useful in developing new effective medicines. Antagonists of purine nucleotide synthesis are the most important, then the class of cardiotonic agents with positive inotropic effects based on 2-aryl IPs derivatives, and finally, IP-2-ones, the new generation of antihypertensive agents which are antagonists of Angiotensin II receptors. Hydrogenated derivatives of IPs like spinaceamines and streptothricines also are of interest. Pesticidal activity of IPs also draws certain attention. Here, we give only a general outline of the biological properties of IPs.

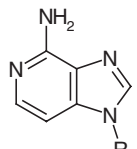
The primary driving force for the development of the chemistry and pharmacology of IP derivatives was the hope of building deazaanalogues of natural purine bases capable of inhibiting purine biosyntheis. These are first of all 1- and 3-deazaadenine (1- and 3-DAA) **8**, **7** and **1–652** and 3-deazaguanine (1- and 3-DAG). Their antibacterial and cytostatic activities were reviewed in (81KG147). Dimmling and Hein were the first to show that 3-DAA **7** was an antibacterial agent (52AF515), and Kidder and Dewey discovered that 1-DAA **8** was capable of inhibiting the growth of the microorganism *Tetrahymena pyriformis* strain W (57MI2). However, 1-DAG analogue **178** did not inhibit bacterial growth obviously due to its extremely low solubility (56JA4130, 57MI2). On the other hand, 1-deazaadenosine (1-DAAS) phosphates acted as an activator for a number of adenosine utilizing enzymes. 3-DAAS **285** is an inhibitor of S-adenosylmethionine-dependent methyltransferases (81MI3) due to its ability to inhibit S-adenosyl-L-homocysteine hydrolase (86JMC138).



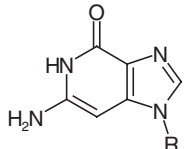
(8)



(652)



(7, 285)



(178, 182)

R = H, R = b-β-ribofuranosyl

There are numerous reports on the biochemistry of 3-DAA (82MI1, 83MI1, 84MI2, 87MI4, 90MI4, 91MI2, 97MI2, 99MI1, 99MI2, 99MI3). The antiviral, anti-influenzal and malaricidal activity of 3-DAAS **285**, as well as its activity *in vivo* against acute inflammations has been reported (79USP4148888, 86JMC138). 3-DAAS is known to be a very effective anti-inflammatory agent with local and systematic effect (when administered orally). It can be used to treat arthritis, including rheumatic arthritis and osteoarthritis, as well as postoperative inflammations, gum inflammation and conjunctivitis. It is most effective in the treatment of acute and chronic arthritis. 3-DAAS has a high therapeutical index that prevents the threat of casual overdose. The preferred daily dose is 0.3–1 mg/kg. It can be administered for several years. 3-DAAS does not possess antipyretic and analgesic activity, and thus it resembles the steroidal anti-inflammatory agents of prednisolone type. It does not produce side effects such as provoking stomach gastritis or inhibiting platelet aggregation, and it does not cause liver problems in contrast to paracetamol (81BRP2074858). Many of 3-DAA benzyl derivatives, for example, 4-(*o*-ClPhCH$_2$NH)-1-Me-IcP, can be used to treat epilepsy, brain infarct, alcohol syndrome, convulsions, and fear state, etc. (83GEP3150486).

However, the most powerful and versatile activity among all the imidazopyridine-like antimetabolites was shown by 3-DAG **178**, its nucleoside **182**, and nucleotides. At the start of research, the low solubility of 3-DAG and its salts, similar to that of 1-DAG, impeded the studies. Fortunately, this obstacle was circumvented by the synthesis of 3-DAG mesylate, well soluble in water (84EUP0103417, 85MI3).

3-DAG base, its nucleosides (3-DAGs) and nucleotides (3-DAGd) represent a class of purine analogues possessing antiviral properties. They are active against the following viral infections in mice: influenza of type A and B, parainfluenza of type 1 (77AAC114, 83JMC286), and their activity exceeds that of ribavirin. The influence of 3-DAG and ribavirin on viral cytopathic effect (CPE) and on the reproduction of rinovirus RV/13 was carefully studied. The ten-times lower concentration of 3-DAG (10 mg/mL) than that of ribavirin was needed for complete (100%) inactivation of CPE (77AAC114).

3-DAG possesses the most powerful activity against rotavirus (82AAC66). Interestingly, 7-β-D-ribofuranosyl-3-DAG shows antibacterial activity against several Gram-negative bacteria with no toxicity to the host (83JMC286). 3-DAG can show higher activity against hard human tumours compared to well-known purine antimetabolites. The same compound, as well as its N-2 deoxyribofuranoside, inhibits the synthesis of DNA and RNA viruses (75JA2916) and L1210 cells leukemia (79JHC1063, 83JMC286, 85MI3). It has been suggested that the antitumour activity of 3-DAG can result from its incorporation into the tumor-cell DNA (83JMC286). It is extremely important that 3-DAG can cross the blood–brain barrier (85MI3). Antiviral activity and resistance to adenosine deaminase was revealed in 1- and 3-β-D-arabinofuranosyl-IcP with amino and other groups in 4 or 6 position of the ring (for example, **653**) (82USP4315000).

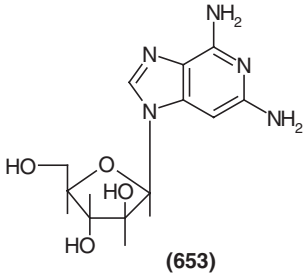
The results obtained with some non-carbohydrate derivatives of 3-DAG and 3-DAA are worth mentioning. For example, the 3-DAG 9-(2-phosphonomethoxyethyl) derivative has shown marked activity against L1210 cells leukemia and DNA-containing viruses (93CCC1419).

9-(2-(*S*)-Hydroxy-3-nonyl)-3-DAG **654** is an active adenosine deaminase (ADA) inhibitor. This inhibition can prevent the deactivation of adenosine analogues used in clinical practice (94JMC305).

1-Cyclopentyl-substituted non-carbohydrate analogues of 3-DAAS, like 1(±)-3-deazaaristeromycin **655**, possess an antiviral activity and inhibit adenosylhomocysteine hydrolase (83USP4387228).

It was noted some time ago, that not only 1- and 3-DAA **8** and **7** and 1- and 3-DAG **652** and **178**, but also their ribofuranosides were capable of inhibiting nucleic acid synthesis. *N*-β-D-ribofuranosides and other glycosides of unsubstituted IbPs and IcPs, as well as their halo and nitro derivatives act similarly but less efficiently. For example, 3-β-D-ribofuranosyl-IbP inhibits the reproduction of Ranikhet disease virus and shows to some extent an anticancer activity. However, the aglycone of IbP also shows definite activity towards *E. coli* phage. But 3-β-D-ribofuranosyl-IcP does not possess any activity (63IJC30). 6-Bromo-IbP, its 2-methyl derivative**,** as well as 4-chloro-2-methyl-IcP have shown poor or very poor antimicrobial activity in contrast to 7-nitro-2-methyl-IcP, which has exhibited a strong suppressive effect upon *Staphylococcus aureus* 209. β-D-ribofuranosyl, β-D-galactopyranosyl and β-D-glucopyranosyl derivatives of the above IPs exhibited strong antimicrobial activity towards *Staph. aureus* 209, *E. coli*, *Proteus vulgaris*, high antifungal effect against *Epidermophyton rubrum*, and glycosides of 4-chloro-IcP inhibit growth of tumours inoculated in mice to 60–70% (75MI2).

Some diamino-IPs are mitotic inhibitors with antitumour activity. Thus, substituted 5,7-diamino-IbP notably extends the lifetime of mice when used in treatment of L1210 leukemia. 4,6-Diamino-IcP and 5-amino-7-chloro-IbP are known to inhibit the proliferation of L1210 cells and exhibit antimitotic activity (87JMC1746, 78JMC112).



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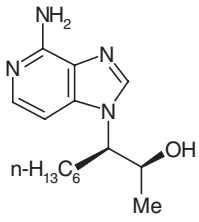

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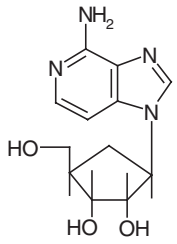
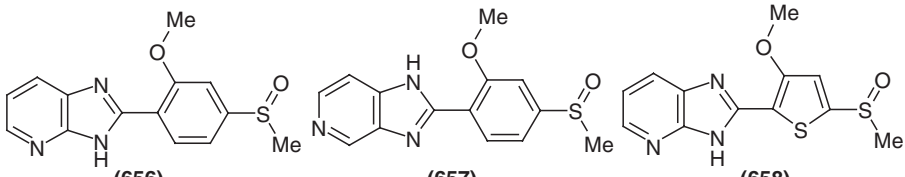


(655)

IbP and especially IcP aryl and hetaryl derivatives constitute a pharmacologically important group of substances. The best known are the substituted 2-aryl-IbPs possessing cardiotonic activity with positive inotropic effect. As a rule, these are N-unsubstituted 2-phenyl IbPs and IbPs containing at the 2 and 4 position of the phenyl ring substituents like alkoxy, alkylthio, alkylsulphinyl, alkylsulphonyl, etc. (82GEP3044497, 82USP4327100, 83BRP2113675, 83GEP3132754, 83GEP3139064, 85GEP3346602, 85JMC717, 85MI6). Out of hundreds of compounds that have been tested for this activity, only IPs with a 2-methoxy-4-methylsulphinylphenyl group turned out to be optimal (82MI4, 83BRP2113675, 83USP4421755, 85JMC717,

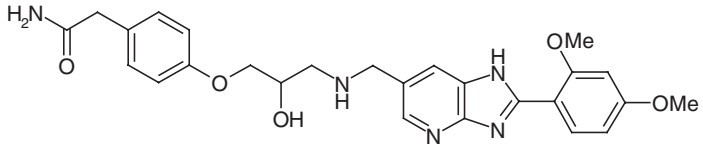
85MI6). It is used under the name "sulmazole" **656** and isomeric IcP **657** is known as "isomazole" (84MI1, 85JMC717, 85MI6, 88MI3).

However, it was found that **657** is 10-fold more efficient compared to **656** both *in vitro* and *in vivo* (85MI6, 85JMC717). Possessing inotropic and vasodilating activity, isomazole has shown a therapeutic effect at very low doses up to LD_{50}, and therefore can be of interest for chronic management of congestive heart failure as a non-catecholamine and non-glycoside substance. The corresponding sulphide (4-SMe) and sulphone (4-SO_2Me) are metabolites of isomazole **657** that also exhibit an inotropic effect (85MI6). The medicinal formula for sulmazole and isomazole has been patented (82USP4327100, 83BRP2113675, 83USP4421755). Biochemical aspects of isomazole and sulmazole action have been reported (94MI7, 95MI1, 95MI4, 95MI6, 95MI7, 96MI2, 96MI3, 97MI1). Thiophene analogue **658** of sulmazole (85MIP379395) with positive inotropic effect was also patented (85MIP379395).



(656) **(657)** **(658)**

Structure **659** was produced as an intramolecular combination of 2-(2,4-dimethoxyphenyl)-IbP similar in structure to sulmazole with atenol, a known cardioselective β_1-adrenoblockador (94JCR(S)426).



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The 2-(2-methoxy-4-sulphinylphenyl) derivatives of 6-hydroxy-IbP (82USP4353909) as well as 4- and 6-oxo-IcPs (85GEP3346602) have been proposed as cardiotonic medicines. It is likely, that the presence of a hydroxy(oxo) group in the IP ring facilitates their catabolism and reduces the pressure on a human organism. 2-(2-Naphtyl)-IPs, including also those with substituents in position 3 of the naphthyl ring and in the heterocycle (5-oxo-IbP, 4-oxo-IcP), exhibited cardiotonic effects (84GEP3225386, 86GEP3445299).

A large series of 2-phenyl-IcPs with various substituents in phenyl (Alk, OAlk, SAlk, SOAlk, SO_2Alk, OH, Halogen, CN, NO_2, NH_2, CF_3, etc.) and hetaryl rings (Alk, Cl), possess bronchodilating, vasodilating and anticoagulant properties (90USP4904785).

2-[3,4,5-(MeO_3)Ph]-1-Me-IcP has spasmolitic activity comparable to that of dibazole, being somewhat less toxic. This compound induces 20- to 30-fold longer hypotension at the same doses as dibazole (97SUP1282506).

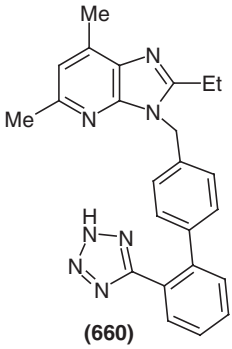
2-(Pyridyl-3 and 4)-IbPs and 2-(pyridyl-4)-IcP exhibited antihypertensive activity. The latter 2-pyridyl-4-IcP also is a strong inhibitor of xanthine oxidase (82USP4336257).

Since the drug tolerance to this compound is high, it may be of interest as a medicine for treatment of gout and hyperuricemia, as well as an antihypertensive agent. IbP and its 1- and 3-substituted derivatives containing 3- and 4-pyridinyl moieties in the pyridine ring exhibited pronounced cardiotonic activity (81USP4276293).

Numerous publications in the 1990 s concerned the synthesis of efficient antihypertensive drugs, analogues of lasortan from the series of IP derivatives. As antagonists of Angiotensin II they were expected to block the receptors of this biogenic octapeptide stronger and longer. The characteristic structural feature of selected IP derivatives exhibiting high antihypertensive efficiency is the presence of a common fragment with losartan, namely, of a biphenyl substituent with a tetrazole ring attached to the terminal phenyl ring in the *o*-position to the first phenyl, the latter linked in turn through a methylene bridge to one of the nitrogen atoms of IP. This structure provides the molecule with the necessary conformational flexibility. The IbP derivative **660** showed considerably superior antihypertensive activity (0.1–0.3 mg/kg), selectivity and duration of action as compared to losartan. The hypertensive effect from a single dose of **660** is conserved over 24–28 hours, also *in vivo* tests, when administered orally or intravenously (91JMC2919, 94TL5775, 94MI1). Many IbP derivatives with the same structure (91USP5053329) have shown antihypertensive activity, including analogue **660**, where instead of a 5-methyl group there is a $(MeO)_2CH$-group along with a 6-Ph group with high conformational flexibility. It was shown that the latter structural feature is decisive for stronger binding of the ligand to an Angiotensin II receptor (94MI3, 96AX(C)1019).

The limited conformational flexibility of a bridging methylene group in IbP **661**, however, did not impede its high antihypertensive efficacy comparable to that of **660**, providing the structure of the imidazole ring in the former is little modified (94MI3).

The introduction of a tetrazolylbiphenyl methyl group and extensive modification of substituents in the structure of this heterocycle resulted in compound **662** with high antihypertensive activity exceeding that of IbP **660**. The corresponding dimethylamide of **662** is two times less active than diethylamide **662** (94JMC1632).



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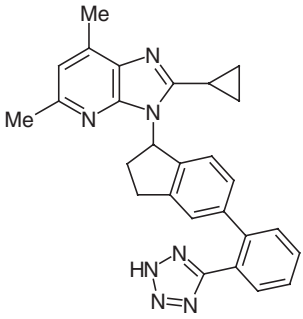

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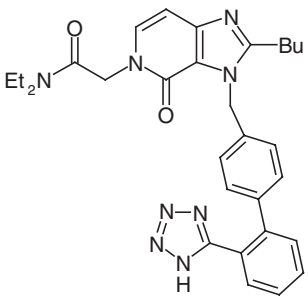

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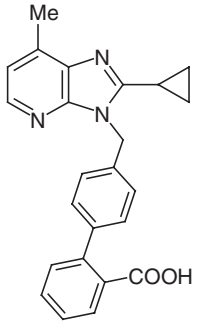
Further modification of the described structure was required to perform balanced binding of Angiotensin receptors like AT_1 and AT_2. It was achieved by the introduction of an amido substituent onto position 6 of the IP ring and by replacement of the tetrazole ring with an acylsulphamide substituent. Compounds of such structure demonstrated high and stable antihypertensive activity both on rats and dogs on oral administration (94MI1).

Introduction of a carboxy group onto the imidazopyridine provides these compounds with insurmountable antagonism towards Angiotensin II and extends the durability of hypertension (94MI2).

The modification of **662** by replacing the tetrazole moiety of the biphenyl chain by a carboxy group results in IbP **663** surpassing captoprile in antihypertensive efficacy and shows promise as a therapeutic agent. The series of IbP derivatives with a 4-hydroxybenzyl group containing halo, nitro, oxy, methyl or *t*-butyl substituents at the 3- or 5- positions was also tested. However, only one, IbP with the 3,5-dichloro-4-hydroxybenzyl substituent, possessed notable antihypertensive activity. Compound **664** was more active than losartan, but inferior to the latter in duration of action (94MI5).

A series of IP's derivatives with a 1,4-dihydropyridine ring with various substituents was studied with respect to the inhibiting activity against the Angiotensin II receptor. Compound **665** was considered to be optimal, and it became the representative of a new class of AT_1-selective agents (94MI4).



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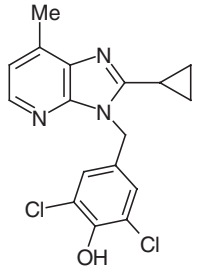

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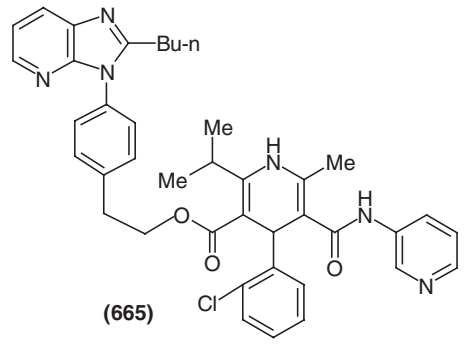

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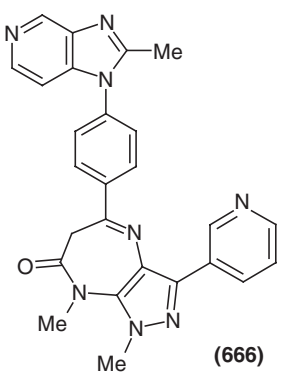
The solution to other important medical problems, i.e., the development of highly effective antagonists for platelet-activating factor (PAF), also depends on the synthesis of complex IP derivatives. PAF is a mediator generated in response to inflammatory or immune stimulation, and it operates by acting on specific receptors located in a variety of inflammatory cell types. The IPs containing diazepine ring **666** (95JMC3524) or 3-acyl indole fragment **667** (98JMC74) were suggested as PAF antagonists capable of reliably blocking the receptors.



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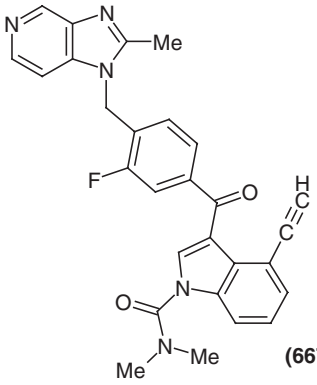

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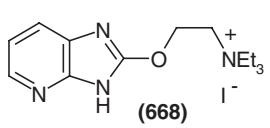
A large number of other IP derivatives possess various pharmacological activity. For example, 2-(*p*-chlorophenyl)-3-Py-2-methyl-IbP exhibits anxiolic and anticonvulsant properties (91USP5066654), and 5-substituted IcP derivatives demonstrate antiplogistic, antiasthmatic, antihemostatic and other activities (91USP4988707, 91USP5019581). The 6-chloro-2-(2,2-dimethyl-3-carboxypropyl)-3-*p*-chlorophenylmethyl-IbP is an orally administrable active antagonist of the TXA_2/PGH_2 receptor, interesting as a possible drug (94JHC73).

Triethylammoniumethyloxy-IbP iodide **668** and oxalates of **669** can cause hypotension. The latter compound also exhibits antiarrhythmic activity (82MI1).

The derivatives of IbP-6-carboxylic acid ethyl ester (e.g., **670** and **671**) (76USP3996233, 77USP4003908, 77USP4043182, 78USP4088654), and analogously substituted IcP-7-carboxylic acid and its ethyl ester, for example, **672**, (76USP3891660), may become central nervous system depressants and anti-inflammatory agents. Moreover, they are capable of increasing the concentration of adenosine 3′,5′-cyclomonophosphate in cells.



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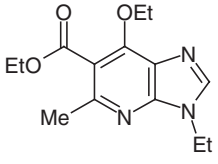

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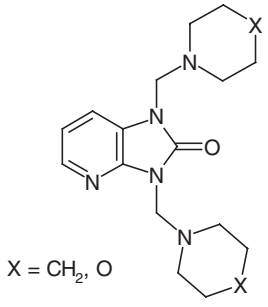

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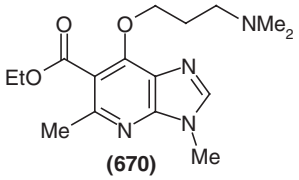

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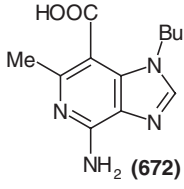

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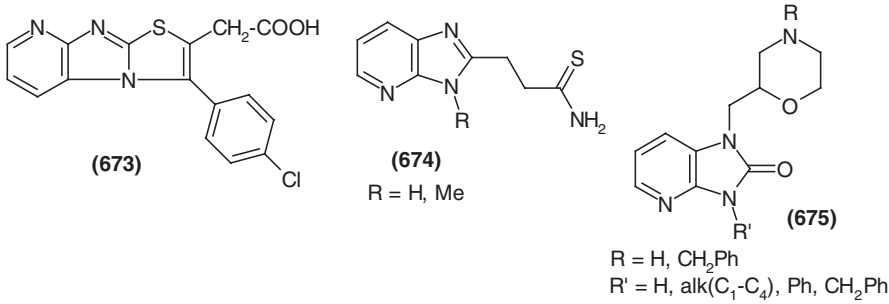
Cyclic sulphides containing the IbP heterocycle in their structure (e.g., **673**) can be used as immunomodulating agents (81USP4293696). IbP-2-propionic acid **674** thioamides showed a significant tuberculostatic effect (89PHA267).



4-(3-methyl-benzo[b]thiophen-2-yl-oxy) and 4-(4-chloro-benzyloxy)-1-methyl-1H-IcPs (83GEP3150486) were suggested to treat epilepsy, brain infarct, alcoholism, fear condition, and convulsions. IbP-2-ones **675** possess an antidepressant effect (79USP4152434), and IbP-2-ones with 3-$Et_2NCH_2CH_2$, pyridyl-3, pyridyl-4 and F-Ph substituents were suggested for treating ulcers and gastritis (79BRP2006758, 81USP4247556).

Other 2-oxo-IbPs with various pyridyl substituents in the imidazole ring have also exhibited anorexigenic and antisecretory activities (80USP4195088). 2-Oxo- and 2-thione derivatives of 3-phenyl-IbP (76GEP2623469, 78JMC965) have shown antipyretic and anti-inflammatory efficacy surpassing that of codeine and not inducing drug dependence. 3-2,4-Di(MeO)Ph-IbP-2-one and 3-(3,4-ethylenedioxyphenyl)-IbP-2-one act similarly (79USP4144341).

A large group of IbP-2-ones or 2-thiones containing a 4- or 3-pyridinyl substituents in positions 5 or 6 are of interest as cardiotonic agents (81USP4294837, 82USP4309537).

Compound 6-Py-4-5-Me-IbP-2-one proved to be the most potent inhibitor of AMP PDE in the nanomolar range (94JMC248).

Compounds with the structure 2-(*m*-MeOPh-CH_2S)-IcP or those related to it are proposed as antiosteoporotic agents. They stimulate the formation of osseous tissue (92USP5081253).

2-Amino derivatives of IPs demonstrated diverse biological activities. Amine 2-NMe_2-6-Py-4-3-Me-IbP also exhibits a high cardiotonic activity. The same function was found in other compounds with a similar structure containing a pyridinyl-4 or pyridinyl-3 group in position 6 (83USP4391811). A series of 2-(piperydyl-4)amino-IbP are antihistaminic agents (80USP4219559).

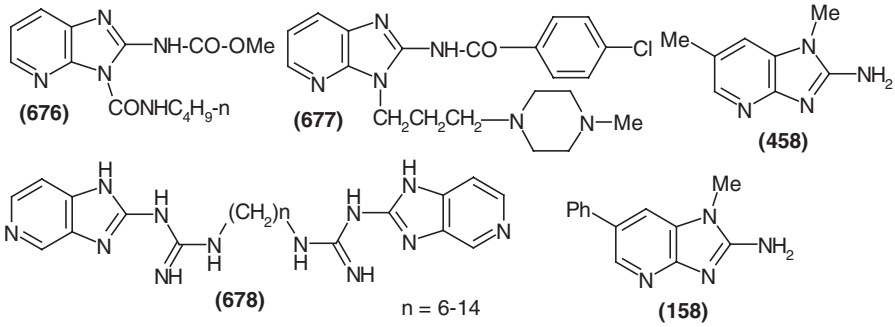
IbP **676** and its close structural analogues show strong effects against parasitic helminthes of animals (75USP3920669, 77BRP1465583).

3-Substituted 2-acylamino-IbPs (e.g., **677**) are claimed to be a new class of anti-inflammatory agents (77USP4059584). Selective antimicrobial, antiseptic and disinfectant action was found in 2-guanidyl-IbP and IcP **678** connected by polymethylene chains (83USP4395552).

In the last 10 years, many publications reported the high mutagenic and carcinogenic activity of some 2-amino-IbP derivatives with relatively simple structure. Among these are, first of all, 2-amino-1,6-dimethyl-IbP and 2-amino-6-phenyl-1-methyl-IbP **158** and **4584** (93JOC7952). It is not so important that these compounds

are toxic because we know quite a number of highly toxic compounds. Of vital significance is the fact that these compounds are widespread in the environment. They are present in cigarette smoke condensate, in diesel exhaust particles, in rain water, in soil and in food, especially in sausage, roasted meat and fish.

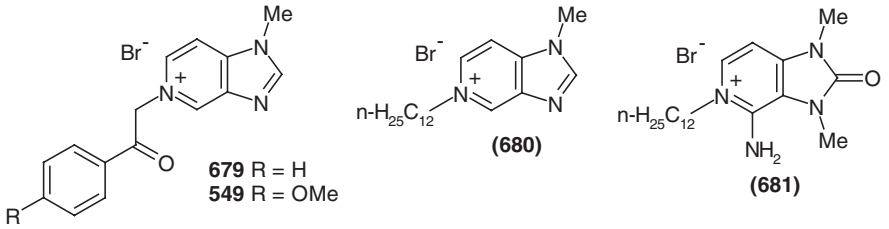
Mutagenic 2-amino-IbP bases **158** and **458** (for example, substituted with two or more methyl groups on the pyridine ring) were believed to appear in food as a result of pyrolysis of amino acids, peptides and proteins and, for example, as a result of thermal condensation involving creatinine, sugars and amino acids present in raw meat and fish (94H529, 94JHC1641). This information is not surprising because the high mutagenic activity of some simple aminopurines is well known (60MI3, 61ZN515).



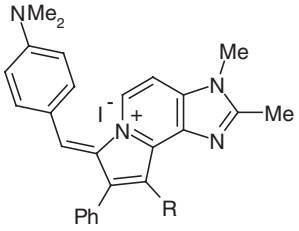
In addition to the pharmacological properties of IPs, we also refer to lesser-known examples of their pesticidal activity. Bromides of 5-phenazyl-1-Me-IcP **679** are of great interest as active agents against classical plague viruses of birds (EHCO-6), as well as against smallpox vaccine (89KFZ56).

Various IcP derivatives have exhibited antimicrobial and fungistatic effects. Salt 5-lauril-1-Me-IcP-2-one is the most efficient and surpasses Furacillin with respect to some microorganisms. Another salt, 4-NH_2-5-lauril-1,3-diMeIcP-2-one bromide, was less active but also less toxic and was more active than Furacillin in a number of cases (88SUP851940).

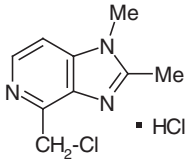
A distyryl derivative of IcP quaternary salt showed somewhat lower bacteriostatic activity compared to bromides **680** and **681** but it was less toxic and possessed more versatile activity (86SUP1048742). Two monostyryl quaternary salts demonstrated a strong fungicidal effect on *Botrytis cinerea*, *Verticillum dohliae*, *Xathomonas maevacearum* (86SUP813921).



Indolizines **682** and **683** readily formed from 4-alkyl(benzyl)-substituted-1,2-dimethyl-IcPs are also effective against *Bacillus antracoides*, *Shigella flexneri* and other microorganisms (86SUP1047148, 89KFZ697). 4-Chloromethyl-1,2-dimethyl-IcP **684** and the product of its modification, 4-amino-1-methyl-IcP-2-one **685** have exhibited high bacteriostatic effect towards *Trichophyton* (86SUP1048743, 97SUP1048745).



682 R = Me, 683 R = Ph



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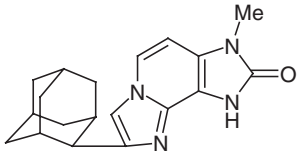
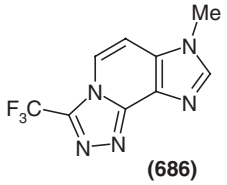
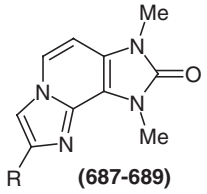


(685)

The first representative of narcotic analgesic agents among the derivatives of condensed IcPs was imidazo[4,5-c]imidazo[1,2-a]pyridine **687** easily prepared from 4-amino-1,3-dimethyl-IcP-2-one. Its activity is four times higher than that of analgine and surpasses promedole more than eight times. Compound **688,** analogue of **687,** is less toxic and somewhat more active than analgine in its analgesic activity, and its antiphlogistic efficiency is much greater than that of the latter (87SUP991716, 97SUP1010846). Compound **689** (87SUP1048746) and imidazo[4,5-c]1,2.4-triazolo[4,3-a]pyridine derivative **686** obtained from 4-hydrazino-1-methyl-IcP (87SUP1094303) has shown spasmolitic activity comparable with that of dibazole.



(686)



687 R = Me
688 R = n-MeOPh
689 R = adamantyl-2

(687-689)

Polyfluoroalkyl derivatives of IbP possessing significant herbicidal properties were described in a series of patents by Doherty (72USP3681369, 74USP3813407, 74USP3813408, 74USP3818022, 76USP3932428, 76USP3961937, 76USP3963734, 76USP4000145, 77USP4042593, 78USP4087432).

The acaricidal effect on bean mite "*Tetranychus urtical Koch*" of a 0.1% solution of 2-thioanilide 1-MeIcP with respect to Keltan as standard (100%) was 80%, for base 2-(4-OH-3-MeOPh)-IcP and phenacylium salt 1-MeIcP (86SUP993620, 98SUP879945) it was 90%. *p*-BrPh-imidazo[4,5-g]indolizine (98SUP879946) showed the same performance as Keltan.

Two 5-phenacylium salts 2-H- and 2-Ph-1MeIcP exhibited a strong insecticidal effect towards room flies comparable with that of Keltan (86SUP915432). *p*-BrPh-imidazo[4,5-g]indolizine proved to be effective against rice weevil (98SUP879946).

A review on the biological activity of IPs cannot be complete without mentioning IcP hydrogenated derivatives, especially spinaceamines (4,5,6,7-tetrahydro-IcPs or SpAs).

In contrast to IPs, the compounds of this group are widely spread in plants and animals, where they perform a variety of biological functions. Unsubstituted SpA, as well as the other heterocyclic amines are present in amphibians skin (Amphibius from Australia and New Guinea), where they are formed from *N*-methyl histamine and likely from spinacine (SpN) through *N*-methyl histidine (64MI2, 76ZN(C)118). SpA differs greatly from histamine in its biological activity. SpA practically does not influence blood pressure and possesses only 15% of the activity of histamine with respect to uterine muscle (21MI1).

Spinacine is still a poorly understood and mysterious natural amino acid. It is a virtually non-toxic substance (89MI1, 92MI1, 97SUP1220307) that can be present in considerable amount in cheese (92MI1, 96MI1). SpN is an active inhibitor of gamma-aminobutyric acid (GABA), but 5-methyl-SpN is two times more active than SpN and is comparble in efficacy with the alkaloid guvacine, a well-known GABA inhibitor. A 3 mg/kg dose of SpN introduced into spinal brain increases the pain threshold in rats for 1 h. Being an inhibitor of GABA capture, SpN depresses interneuronic transmission in spinal cord synapses and ensures anesthetization at subarachnoidal administration (88KFZ20, 97SUP1220307).

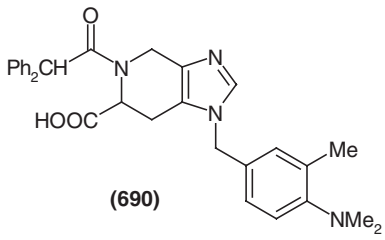
Recently, SpN derivative **690** showed an antagonistic effect against the Angiotensin II receptor of type AT_2 (90MI3, 91JHC97, 91JMC3248, 94MI1).

Both SpA and SpN exhibited a broad range of antimicrobial and fungistatic activity (on 16 strains) (52AF515), but this activity was only moderate. Possessing bacteriological activity, SpA functions as a protective agent for the skin of amphibias. It suppresses *Staphylococcus aureus* at 0.6% concentration (70ZN1451).

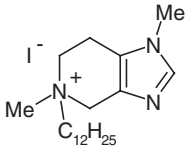
SpA quaternary salt **562** showed antimicrobial and fungistatic activity with a quite high therapeutic index (86SUP1039174).

The dichloride of 1,5-diMeSpA possesses antiphlogistic and analgesic properties largely exceeding some parameters of analgine (81UP1).

5-(*β*-Oxyphenyl)-1-methyl-SpA and its nitro derivative (97SUP1067801, 97SUP1387375) demonstrate pronounced analgesic and prolonged anti-inflammatory effect. Compound 5-(*γ*, *γ*-diMe-*β*-HO)-1-Me-SpA greatly surpasses dibazole in hypotensive quality and is three times less toxic (83UP1).



(690)



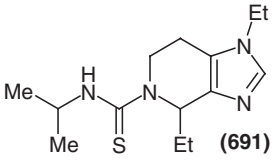
(562)

Even higher antihypertensive, hypotensive, spasmolitic and sedative activity is observed in SpA **544,** and it can be compared to clophelin, but **544** does not cause

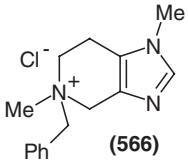
cardiodepression in contrast to the latter (98MI1). Miotropic and spasmolitic effects are typical of 3,4-$(MeO)_2$Ph-SpA (82UP1) and similar to those of dibazole. SpA derivatives containing a thiourea fragment in their structure exhibit antiulcer and antisecretory activity.

Compound **691** is the most active in this respect. This slightly toxic compound is able to reliably inhibit gastric and duodenal ulcers. Its drug tolerance is good, and it does not cause any pathological changes after treatment. One of the advantages of this compound is the lack of anticholinergic activity (80SUP791241, 84AF1467, 85MI1).

Quaternary salt 5-benzylchloride-1,5-dimethyl-SpA **566** exhibits a fairly high acarycidal effect towards spider ticks (83SUP879944).



(691)



(566)

Much attention of Soviet researchers between 1950–1970 was drawn to the biological activity of streptothricines (StTs). The antiviral, antimicrobial and pesticide activity of various StT-containing agents were studied extensively. But due to their high toxicity and low therapeutic index further studies on the utilization of StTs in medicine were not done. Nevertheless, it was shown that StTs by toxicity and antiviral activity were arranged in alphabetical order: A > B > C > D > F. They have shown low activity against herpetic infection in mice. Repeated administration of an StTs-containing agent to mice infected by influenza of B type increased their lifetime from 2 to 2.4 times (69MI3). StTs have shown a phagocytic effect on some bacteriophages. With respect to staphilofag line 1623 *in vivo* StTs by their inhibiting action are arranged in alphabetical order, i.e. A > B > C > D > F (69MI3).

StTs-contaning agents surpass other antibiotics by their bacteriostatic activity against intestinal bacteria (50MI1). The resistance of *E. coli* bacteria against StTs was studied. As shown for 352 *E. coli* cultures, their sensitivity to StTs were within 0.5–2 ID units (50MI2), but did not exceed 8 ID units (50MI3).

StTs have been applied in agriculture as pesticides but have a disadvantage in their persistence in the environment (75MI2).

VI. Imidazopyridines in Photography

IPs and their derivatives are known to be used in color photography as antifoggants, silver halide development accelerators, as well as photographic layer stabilizers.

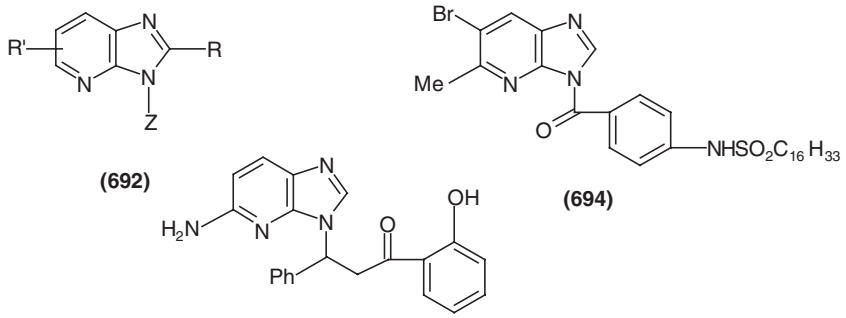
IPs **38,** 6-ClIbP and 6-Cl-2-MeIbP were claimed (69USP3473924) to prevent fogging during the development process and for diffussion transfer of an image.

Compounds **1** and **8** can be used as silver halide development accelerators. Their advantage as accelerators lies in their ability to reduce or to control the induction

period of the film in developers containing hydroquinone. Other advantages include the use of a lesser amount of antifoggant, acceleration of development, and a longer shelf-life of the developer (84EUP0034038).

In order to obtain images characterized by low fog and high contrast at high sensitivity and maximum density, ensuring silver saving compounds 5-R-6-Cl-2-Me-IbP, 5-MeOOC-IbP were suggested as additives to the developer (81GEP3032607).

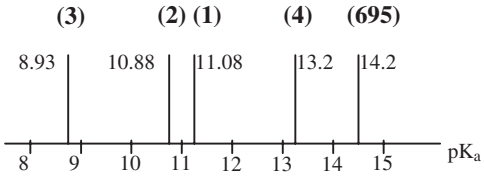
The problem of making antifoggants for silver halide photographic emulsions that would impart increased protection against fogging over a wide range of temperatures was solved by introducing deactivating substituents into antifoggant structures. Compounds like **692** proper do not possess antifogging activity, but they are precursors of antifoggants, since they readily eliminate protective group (Z) in an alkali medium, especially on increasing the temperature. For example, the rate of precursor hydrolysis doubles on increasing the temperature by 10 °C. Thus the introduction of protective group (Z) into the antifoggant molecule prevents untimely reaction between silver halide and antifoggant agent. The structures of some antifoggant agent precursors (82GEP2118933) are presented below (**693**, **694**).



VII. Conclusion

The IP structure occupies an intermediate position between those of benzimidazole and purine and to some extent the structural similarities are reflected in their common chemical properties.

The reported (66MI1) ionization constant of their acidic NH forms for the series purine **3**, IcP **2**, IbP **1**, benzimidazole **4** and imidazole **695** when plotted on a one-dimensional axis gives the following sequence:



In this sequence, the pKa of IbP **1** is placed almost exactly between those for purine **3** and benzimidazole **4**, and IcP **2** is somewhat closer to purine. These ionization constants give some insight into the influence of the fused rings on the acidity of the imidazole NH. Imidazo[4,5-b]pyridines, and imidazo[4,5-c]-pyridines have more in common with purine in terms of molecular structure and chemical properties than with benzimidazole.

Acknowledgement

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References

13MI1 J. Wellisch, *Biochem. Z.*, **49**, 173 (1913) [Chem. Zentrabl. **84.I**, 1607 (1913)].

21MI1 H. H. Dale and H. W. Dudley, *J. Pharmacol. Exp. Ther.*, **18**, 103 (1921).

24JBC303 A. Ch. Chibnall, *J. Biol. Chem.*, **61**, 303 (1924).

27CB766 A. E. Chichibabin and A. W. Kirsanov, *Chem. Ber.*, **60**, 766 (1927).

31JIC241 V. G. Namjoshi and S. Dutt, *J. Ind. Chem. Soc.*, **8**, 241 (1931).

36CB2593 O. Schickh, A. Binz, and A. Schulz, *Chem. Ber.*, **69**, 2593 (1936).

36MI1 D. Ackermann and M. Mohr, *Z. Biol.*, **98**, 73 (1936).

37JOC260 H. W. Post and E. R. Erickson, *J. Org. Chem.*, **2**, 260 (1937).

38CB2347 R. Weidenhagen and U. Weeden, *Chem. Ber.*, **71B**, 2347 (1938).

41MI1 D. Ackermann and E. Müller, *Z. Physiol. Chem.*, **268**, 277 (1941).

42CB1936 R. Weidenhagen and G. Train, *Chem. Ber.*, **75**, 1936 (1942).

44BJ309 A. Neuberger, *Biochem. J.*, **38**, 309 (1944).

46JPJ31 T. Takahashi and S. Yajima, *J. Pharm. Soc. Japan*, **66**, 31 (1946).

47JA1151 J. Bernstein, B. Stearns, E. Show, and W. A. Lott, *J. Am. Chem. Soc.*, **69**, 1151 (1947).

48JA3429 D. Heyl, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **70**, 3429 (1948).

48JA3669 D. Heyl, E. Luz, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **70**, 3669 (1948).

48JCS1389 V. Petrov and J. Saper, *J. Chem. Soc.*, 1389 (1948).

48JCS2240 A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948).

48RTC29 F. Kogl, G. M. van der Want, and C. A. Salemink, *Recl. Trav. Chim. Pays–Bas*, **67**, 29 (1948).

49JA1885 J. R. Vaughan Jr, J. Krapcho, and J. P. English, *J. Am. Chem. Soc.*, **71**, 1885 (1949).

49MI1 D. D. Ackermann and S. Skraup, *Z. Physiol. Chemie*, **284**, 129 (1949) [*CA* **45**, 621b (1951)].

49MI2 S. Skraup and J. Alt, *Z. Physiol. Chemie*, **284**, 132 (1949) [*CA* **45**, 621d (1951)].

49RTC1013 C. A. Salemink and G. M. van der Want, *Recl. Trav. Chim. Pays–Bas*, **68**, 1013 (1949).

50JOC1278 G. B. Bachman, G. E. Bennett, and R. S. Barker, *J. Org. Chem.*, **15**, 1278 (1950).

50MI1 Z. G. Pershina, *Acad. Med. Sciences Transactions. Chemotherapy of Bacterial Infections*, **5** (1), 37 (1950).

50MI2 M. N. Sinyushina, *Acad. Med. Sciences Transactions. Chemotherapy of Bacterial Infections*, **5** (1), 56 (1950).

50MI3 D. G. Kudlay, *Acad. Med. Sciences Transactions. Chemotherapy of Bacterial Infections*, **5** (1), 63 (1950).

51CRV397 J. Wright, *Chem. Rev.*, **48**, 397 (1951).

51ZOB884 A. M. Simonov and P. A. Uglov, *Zh. Obshch. Khim.*, **21**, 884 (1951).

52AF515 T. Dimmling and H. Hein, *Arzneim.-Forsch.*, **2**, 515 (1952).

52CB1012 F. Korte, *Chem. Ber.*, **85**, 1012 (1952).

53JOC534 E. Ochiai, *J. Org. Chem.*, 534 (1953).

54JA566 H. E. Carter, R. K. Clark, P. Kohn, J. W. Rothrock, W. R. Taylor, C. A. West, G. B. Whitfield, and W. G. Jackson, *J. Am. Chem. Soc.*, **76**, 566 (1954).

54JA6073 A. Bendich, P. J. Russel Jr, and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).

54JCS2071 S. F. Mason, *J. Chem. Soc.*, 2071 (1954).

55JA5488 H. Walba and R. W. Isensee, *J. Am. Chem. Soc.*, **77**, 5488 (1955).

56JA4130 D. G. Markees and G. W. Kidder, *J. Am. Chem. Soc.*, **78**, 4130 (1956).

56JCS4683 A. Albert, Ch. Pedersen,, *J. Chem. Soc.*, 4683 (1956).

57AP20 A. Dornow and O. Hahmann, *Arch. Pharm. (Weinheim, Ger.)*, **290**, 20 (1957).

57JA670 B. S. Gorton and W. Shive, *J. Am. Chem. Soc.*, **79**, 670 (1957).

57JA6421 H. Graboyes and A. R. Day, *J. Am. Chem. Soc.*, **79**, 6421 (1957).

57JCS442 J. W. Clark-Lewis and M. J. Thompson, *J. Chem. Soc.*, 442 (1957).

57MI1 A. R. Day, *Trans. N.Y. Acad. Sci.*, **20**, 3 (1957) [*CA* **52**, 8126c (1958)].

57MI2 G. W. Kidder and V. C. Dewey, *Arch. Biochem. Biophys.*, **66**, 486 (1957) [*CA* **51**, 9019g (1957)].

58CB1834 A. Dornow and E. Hinz, *Chem. Ber.*, **91**, 1834 (1958).

59JCS3157 D. Harrison and A. C. B. Smith, *J. Chem. Soc.*, 3157 (1959).

59JOC1455 M. Israel and A. R. Day, *J. Org. Chem.*, **24**, 1455 (1959).

60CPB539 T. Takahashi, K. Kanematsu, R. Ohishi, and T. Mizutani, *Chem. Pharm. Bull. (Tokyo)*, **8**, 539 (1960).

60JCS2369 P. Biddle, E. S. Lane, and J. L. Willans, *J. Chem. Soc.*, 2369 (1960).

60MI1 S. K. Chatterjee, M. M. Dhar, N. Anand, and M. L. Dhar, *J. Sci. Ind. Res. (India)*, **19c**, 35 (1960).

60MI3 A. Wacker, S. Kirschfeld, and L. Trager, *J. Mol. Biol.*, **2**, 241 (1960) [*CA* **55**, 3706e (1961)].

60ZOB590 A. M. Simonov and N. D. Vitkevich, *Zh. Obshch. Khim.*, **30**, 590 (1960).

61JA4296 H. E. Carter, C. C. Sweeley, E. E. Daniels, J. E. McNary, C. P. Schaffner, C. A. West, E. E. van Tamelen, J. R. Dyer, and H. A. Whaley, *J. Am. Chem. Soc.*, **83**, 4296 (1961).

61MI1 R. H. Mizzoni, in *Pyridine and its Derivatives* (E. Klingsberg, ed.), pt. 2, p. 479. NewYork, London (1961).

61USP3004978 A. Hunger, J. Kebrle, A. Rossi, and K. Hoffmann, U.S. Pat. 3,004,978 (1961) [CA **56**, 4770i (1962)].

61ZN515 H. Gottschling and E. Freese, *Z. Naturforsch*, **16B**, 515 (1961) [*CA* **56**, 3902i (1962)].

62JCS2379 J. W. Clark-Lewis and R. P. Singh, *J. Chem. Soc.*, 2379 (1962).

62JPR199 Von W. Knobloch and H. Kuhne, *J. Prakt. Chemie*, **17**, 199 (1962).

63CPB265 Y. Mizuno, M. Ikehara, T. Itoh, and K. Saito, *Chem. Pharm. Bull. (Tokyo)*, **11**, 265 (1963).

63E346 V. Erspamer, T. Vitali, M. Roseghini, and J. M. Cei, *Experientia*, **19**, 346 (1963).

63IJC30 P. C. Jain, S. K. Chatterjee, and N. Anand, *Indian J. Chem.*, **1**, 30 (1963).

63JCS1666 O. Meth-Cohn, R. K. Smalley, and H. Suschitzky, *J. Chem. Soc.*, 1666 (1963).

63JOC1837 Y. Mizuno, M. Ikehara, T. Itoh, and K. Saito, *J. Org. Chem.*, **28**, 1837 (1963).

63MI1 V. I. Uspensky, *Histamine*, Moscow, 1963.

63MI3 P. Bassignana, C. Cogroasi, and M. Candino, *Ann. Chim.*, **53**, 1677 (1963) [*CA* **60**, 1238c (1964)].

64CPB866 Y. Mizuno, T. Itoh, and K. Saito, *Chem. Pharm. Bull.*, **12**, 866 (1964).

64G296 T. Vitali and G. Bertaccini, *Gazz. Chim. Ital.*, **94**, 296 (1964).

64JOC2611 Y. Mizuno, T. Itoh, and K. Saito, *J. Org. Chem.*, **29**, 2611 (1964).

64JOC3209 A. Ginner-Sorolla, E. Thom, and A. Bendich, *J. Org. Chem.*, **29**, 3209 (1964).

64JOC3403 D. L. Garmaise and J. Komlossy, *J. Org. Chem.*, **29**, 3403 (1964).

64MI1 D. Ackermann and G. Hoppe-Seyler, *Z. Physiol. Chem.*, **336**, 283 (1964).

64MI2 V. Erspamer, T. Vitali, M. Roseghini, and J. M. Cei, *Arch. Biochem. Biophys.*, **105**, 620 (1964) [*CA* **61**, 4755a, (1964)].

64RS718 M. Nardelli, T. Vitali, and F. Mossini, *Ric. Sci.*, **7**, 718 (1964).

64RZC887 Z. Talik and B. Brekiesz, *Rocz. Chem.*, **38**, 887 (1964).

65FES634 T. Vitali, P. Mossini, and G. Bertaccini, *Farmaco Ed. Sci.*, 634 (1965).

65JHC196 R. J. Rousseau and R. K. Robins, *J. Heterocycl. Chem.*, **2**, 196 (1965).

65JMC296 M. M. Vohra, S. N. Pradhan, P. C. Jain, S. K. Chatterjee, and N. Anand, *J. Med. Chem.*, **8**, 296 (1965).

65JMC708 J. A. Montgomery and K. Hewson, *J. Med. Chem.*, **8**, 708 (1965).

65JOC259 V. J. Grenda, R. E. Jones, G. Gal, and M. Sletzinger, *J. Org. Chem.*, **30**, 259 (1965).

65JOC4066 Y. Mizuno, N. Ikekawa, T. Itoh, and K. Saito, *J. Org. Chem.*, **30**, 4066 (1965).

65KG621 I. Ya. Postovskiy and N. N. Vereshchagina, *Khim. Geterotsikl. Soedin.* (4), 621 (1965).

65KPS42 P. D. Reshetov and A. S. Khokhlov, *Khim. Prir. Soedin.* (1), 42 (1965).

65KPS117 P. D. Reshetov, Tz. A. Egorov, and A. S. Khokhlov, *Khim. Prir. Soedin.* (2), 117 (1965).

65MI1 Z. N. Nazarova (ed.), "*Outlines of the Chemistry of Azoles*" Rostov-on-Don, Izd. Rostovsk. Univ. (1965) [*CA* **64**, 15890c (1966)].

65SWP386442 A. Hunger, H. Keberle, A. Rossi, and K. Hoffmann, Swiss. Pat. 386,442 (1965) [*CA* **63**, P14876c (1965)].

66B756 R. J. Rousseau, L. B. Townsend, and R. K. Robins, *Biochemistry*, **5**, 756 (1966).

66CB244 A. Dornow and H. Plessen, *Chem. Ber.*, **99**, 244 (1966).

66CB254 A. Dornow, H. Plessen, and R. Huischen, *Chem. Ber.*, **99**, 254 (1966).

66IJC403 P. C. Jain, S. K. Chatterjee, and N. Anand, *Indian J. Chem.*, **4**, 403 (1966).

66JCS(B)285 G. B. Barlin, *J. Chem. Soc. (B)*, 285 (1966).

66JCS(C)80 R. K. Smalley, *J. Chem. Soc. (C)*, 80 (1966).

66JMC105 J. A. Montgomery, K. Kathleen, and K. Hewson, *J. Med. Chem.*, **9**, 105 (1966).

66JOC1295 W. W. Paudler and H. L. Blewitt, *J. Org. Chem.*, **31**, 1295 (1966).

66JOC2380 F. B. Stocker, M. W. Fordice, J. K. Larson, and J. H. Thorstenson, *J. Org. Chem.*, **31**, 2380 (1966).
66JPR274 Von U. Wallwitz, H. Schmidt, and W. Gosda, *J. Prakt. Chemie*, **32**, 274 (1966).
66MI1 A. Albert, in *"Physical Methods in Heterocyclic Chemistry"* (A. R. Katritzky ed.), p. 109, Khimiya, Moskow-Leningrad (1966).
67FES821 T. Vitali, F. Mossini, and G. Bertaccini, *Farmaco Ed. Sci.*, **22**, 821 (1967) [*CA* **68**, 87234e (1968)].
67JCS(C)33 B. C. Ennis, G. Holan, and E. L. Samuel, *J. Chem. Soc. (C)*, 33 (1967).
67JHC157 F. H. Case, *J. Heterocycl. Chem.*, **4**, 157 (1967).
67JHC483 F. H. Case and L. Kennon, *J. Heterocycl. Chem.*, **4**, 483 (1967).
67JOC2430 W. W. Paudler and J. E. Kuder, *J. Org. Chem.*, **32**, 2430 (1967).
67RZC1887 B. Brekiesz-Lewandowska and Z. Talik, *Rocz. Chem.*, **41**, 1887 (1967).
67SUP201410 Yu. M. Yutilov, R. M. Bystrova and N. F. Kazarinova, USSR Pat. 201,410 (1967).
67SUP207143 H. E. Dealtry, J. T. Newbold and A. Persival, USSR Pat. 207,143 (1967)
68CPB2011 Y. Mizuno, S. Tazawa, and K. Kageura, *Chem. Pharm. Bull.*, **16**, 2011 (1968).
68IJC123 P. C. Jain and N. Anand, *Indian J. Chem.*, **6**, 123 (1968).
68JOC2543 F. M. Hershenson, L. Bauer, and K. F. King, *J. Org. Chem.*, **33**, 2543 (1968).
68KG953 R. M. Bystrova and Yu. M. Yutilov, *Khim. Geterotsikl. Soedin.* (5), 953 (1968).
68KG954 Yu. M. Yutilov and R. M. Bystrova, *Khim. Geterotsikl. Soedin.* (5), 954 (1968).
68MI1 V. I. Minkin, O. A. Osipov, and Yu. A. Zhdanov, *Dipole Moments in Organic Chemistry*, Khimiya, Leningrad (1968) [*CA* **70**, 67471t (1969)].
68RZC1641 A. Nawojski, *Rocz. Chem.*, **42**, 1641 (1968).
69JHC735 M. Israel, L. C. Jones, and A. R. Day, *J. Heterocycl. Chem.*, **6**, 735 (1969).
69JHC759 W. Brooks and A. R. Day, *J. Heterocycl. Chem.*, **6**, 759 (1969).
69KG378 R. M. Bystrova and Yu. M. Yutilov, *Khim. Geterotsikl. Soedin.*, **2**, 378 (1969).
69MI2 R. K. Robins, in *"Heterocyclic Compounds"* (R. C. Elderfield ed.), Vol. 8, p. 130, Mir, Moscow (1969).
69MI3 K. I. Germanova and T. Ya. Goncharskaya, *Antibiotics*, **14**, 137 (1969).
69MI4 O. I. Voronina, K. I. Shutova, I. I. Tovarova, and A. S. Khokhlov, *Antibiotics*, **14**, 1063 (1969) [*CA* **72**, 77387a (1970)].
69RTC1263 K. B. De Roos and C. A. Salemink, *Rec. Trav. Chim. Pays–Bas.*, **88**, 1263 (1969).
69RZC573 A. Nawojski, *Rocz. Chem.*, **43**, 573 (1969).
69RZC979 A. Nawojski, *Rocz. Chem.*, **43**, 979 (1969).
69USP3473924 H. G. Rogers, U.S. Pat. 3,473,924 (1969).
70CPB1685 M. Yanai, T. Kinoshita, S. Takeda, M. Mori, H. Sadaki, and H. Watanabe, *Chem. Pharm. Bull. (Japan)*, **18**, 1685 (1970).
70KG228 A. V. Kazymov, L. P. Shchelkina, L. V. Ivanova, N. V. Monich, and A. F. Vompe, *Khim. Geterotsikl. Soedin.* (2), 228 (1970).
70KG1146 Yu. M. Yutilov and R. M. Bystrova, *Khim. Geterotsikl. Soedin.*, 1146 (1970).

70MI1 L. Del Corona, G. G. Massaroli, and G. Signorelli, *Boll. Chim. Farm.*, **109**, 665 (1970) [*CA* **75**, 20297d (1971)].

70MI2 N. K. Kochetkov, E. I. Budovsky, E. D. Sverdlov, N. A. Simukova, M. F. Turchinsky, and V. N. Shibaev, Organic Chemistry of Nucleic Acids, Khimiya, Moscow (1970).

70UP1 Yu. M. Yutilov and R. M. Bistrova, unpublished results (1970).

70ZN1451 G. Habermehl and H. -J. Preusser, *Z. Naturforsch*, **25b**, 1451 (1970).

71AJC2389 E. J. Browne, *Aust. J. Chem.*, **24**, 2389 (1971).

71CB344 H. Rochling and K. H. Buchel, *Chem. Ber.*, **104**, 344 (1971).

71G625 G. D. Andretti, L. Cavalca, and P. Sgarabotto, *Gazz. Chim. Ital.*, **101**, 625 (1971).

71GBP1114199 G.B. Pat. 1,114,199 (1971).

71JHC797 M. Israel and L. C. Jones, *J. Heterocycl. Chem.*, **8**, 797 (1971).

71KG279 A. V. Kazymov, L. P. Shchelkina, and N. G. Kabirova, *Khim. Geterotsikl. Soedin.* (2), 279 (1971).

71KG428 Yu. M. Yutilov and I. A. Svertilova, *Khim. Geterotsikl. Soedin.*, 428 (1971) [*CA* **76**, 3755 (1972)].

71KG693 A. V. Kazymov and L. P. Shchelkina, *Khim. Geterotsikl. Soedin.* (5), 693 (1971).

71KG1436 Yu. M. Yutilov, N. R. Kalnitsky, and R. M. Bistrova, *Khim. Geterotsikl. Soedin.* (10), 1436 (1971).

71KG1561 A. V. Kazymov, L. P. Shchelkina, N. G. Kabirova, and A. F. Vompe, *Khim. Geterotsikl. Soedin.* (11), 1561 (1971).

71LA158 G. Cleve, H. Gibian, G. -A. Hoyer, D. Rahtz, E. Schroder, and G. Schulz, *Liebigs Ann. Chem.*, **747**, 158 (1971).

71MI2 P. M. Dzadzic, B. L. Bastic, and M. V. Piletic, *Glas. Hem. Drus. Beograd*, **36**, 137 (1971) [*CA* **78**, 16096 g (1973)].

71RTC654 K. B. De Roos and C. A. Salemink, *Recl. Trav. Chim. Pays–Bas*, **90**, 654 (1971).

71RTC1166 K. B. De Roos and C. A. Salemink, *Recl. Trav. Chim. Pays–Bas*, **90**, 1166 (1971).

72BSF2916 J. Elguero, A. Fruchier, and S. Mignonac-Mondon, *Bull. Soc. Chim. Fr.*, 2916 (1972).

72CPB2264 M. Ogata and H. Matsumoto, *Chem. Pharm. Bull. (Japan)*, **20**, 2264 (1972).

72DOK1119 K. I. Shutova and A. S. Khokhlov, *Dokl. Acad. Nauk SSSR*, **205**, 1119 (1972).

72JCS(CC)652 B. W. Bycroft and T. J. King, *J. Chem. Soc. Chem. Commun.*, 652 (1972).

72KG683 N. K. Beresneva, E. R. Zahs, L. S. Efros, and V. M. Treger, *Khim. Geterotsikl. Soedin.* (5), 683 (1972).

72RTC650 J. Schelling and C. A. Salemink, *Recl. Trav. Chim. Pays–Bas*, **91**, 650 (1972).

72SUP351851 Yu. M. Yutilov and I. A. Svertilova, USSR Pat. 351851 (1972) [*CA* **78**, 58416s (1973)].

72USP3681369 G. O. P. Doherty, U.S. Pat. 3,681,369 (1972) [*CA* **77**, 140073r (1972)].

73JCS(D)323 A. Braibanti, F. Dallavalle, E. Leporati, and G. Mori, *J. Chem. Soc., Dalton Trans.*, **3**, 323 (1973).

73JCS(P1)1615 A. Albert and H. Mizuno, *J. Chem. Soc., Perkin Trans. 1*, **15**, 1615 (1973).

73JCS(P1)1620 A. Albert and W. Pendergast, *J. Chem. Soc., Perkin Trans. 1*, **15**, 1620 (1973).

73JCS(P1)1625 A. Albert and W. Pendergast, *J. Chem. Soc. Perkin Trans. 1*, **15**, 1625 (1973).

73JCS(P1)1794 A. Albert and W. Pendergast, *J. Chem. Soc. Perkin Trans. 1*, **16**, 1794 (1973).
73JMC292 C. Temple Jr., B. M. Smith, R. D. Elliott, and J. A. Montgomery, *J. Med. Chem.*, **16**, 292 (1973).
73JOC613 C. J. Temple, B. H. Smith, and J. A. Montgomery, *J. Org. Chem.*, **38**, 613 (1973).
73KG138 Yu. M. Yutilov and I. A. Svertilova, *Khim. Geterotsikl. Soedin.* (1), 138 (1973) [*CA* **78**, 97547 (1973)].
73KG570 R. M. Bystrova and Yu. M. Yutilov, *Khim. Geterotsikl. Soedin.* (4), 570 (1973) [*CA* **79**, 31981 (1973)].
73S1 F. Minisci, *Synthesis*, 1 (1973).
73UKZ274 N. S. Miroshnichenko, O. I. Shkrebtiy, and A. V. Stezenko, *Ukr. Khim. Zh. (Russ. Ed.)*, **39** (3), 274 (1973) [*CA* **79**, 19020j (1973)].
73UKZ350 N. S. Miroshnichenko, I. G. Ryabokon, and A. V. Stezenko, *Ukr. Khim. Zh. (Russ. Ed.)*, **39** (4), 350 (1973).
73UKZ703 A. V. Stezenko and M. S. Miroshnichenko, *Ukr. Khim. Zh. (Russ. Ed.)*, **39** (7), 703 (1973).
74AHC123 F. Minisci, *Adv. Heterocycl. Chem.*, **16**, 123 (1974).
74CRV279 P. N. Preston, *Chem. Rev.*, **74**, 279 (1974).
74JHC233 R. J. Rousseau, J. A. May Jr., R. K. Robins, and L. B. Townsend, *J. Heterocycl. Chem.*, **11**, 233 (1974).
74MI1 Yu. M. Yutilov and R. M. Bystrova, XII Ukrainian Republic Conference on Organic Chemistry, Abstracts, Uzgorod (1974), p. 46.
74MI2 Yu. M. Yutilov, R. M. Bystrova, and I. A. Svertilova, XII Ukrainian Republic Conference on Organic Chemistry, Abstracts, Uzgorod (1974), p. 120.
74RTC3 R. de Bode and C. A. Salemink, *Rec. Trav. Chim. Pays–Bas*, **93**, 3 (1974).
74TL1413 T. Goto and T. Ohgi, *Tetrahedron Lett.*, **15**, 1413 (1974).
74TL1417 S. Kusumoto, S. Tsuji, and T. Shiba, *Tetrahedron Lett.*, **15**, 1417 (1974).
74UKZ258 N. S. Miroshnichenko, A. S. Kovalenko, and A. V. Stezenko, *Ukr. Khim. Zh. (Russ. Ed.)*, **40** (3), 258 (1974).
74UP1 Yu. M. Yutilov and R. M. Bystrova, unpublished results (1974).
74USP3813407 G. O. P. Doherty, U.S. Pat. 3,813,407 (1974) [*CA* **81**, 49685p (1974)].
74USP3813408 G. O. P. Doherty and K. H. Fuhr, U.S. Pat. 3,813,408 (1974).
74USP3818022 G. O. P. Doherty, U.S. Pat. 3,818,022 (1974).
75JA2916 P. D. Cook, R. J. Rousseau, A. M. Mian, R. B. Meyer, P. Dea, G. Ivanovics, D. G. Streeter, J. T. Witkowski, M. G. Stout, L. N. Simon, R. W. Sidwell, and R. K. Robins, *J. Am. Chem. Soc.*, **97**, 2916 (1975).
75KG90 N. G. Korzhenevskaya, E. V. Titov, Yu. M. Yutilov, and R. M. Bistrova, *Khim. Geterotsikl. Soedin.*, **90** (1975).
75KG1389 Yu. M. Yutilov and L. I. Kovaleva, *Khim. Geterotsikl. Soedin.* (10), 1389 (1975) [*CA* **84**, 43936 (1976)].
75MI2 L. G. Brantsevich, N. S. Miroshnichenko, A. V. Stetsenko, A. T. Slabospizka, and V. V. Chekmacheva, *Microbiol. J.*, **37**, 635 (1975) [*CA* **84**, 25886r (1976)].
75UP Yu. M. Yutilov and O. G. Eilazyan, unpublished results (1975).
75USP3920669 H. Kristinsson, A. Hubele and E. Aufderhaar, U.S. Pat. 3,920,669 (1975) [*CA* **82**, 4256d, (1973)].
76AHCS(1)529 J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem. Supplement*, **1**, 529 (1976).

76GEP2623469 R. L. Clark, A. A. Pessolano and T. -Y. Shen, Germ. Pat. 2,623,469 (1976) [*CA* **86**, 106592k (1977)].

76H127 G. G. Habermehl and W. Escy, *Heterocycles*, **5**, 127 (1976).

76JA1492 P. D. Cook, R. J. Rousseau, A. M. Mian, P. Dea, R. B. Meyer, and R. K. Robins, *J. Am. Chem. Soc.*, **98**, 1492 (1976).

76KG1252 Yu. M. Yutilov and I. A. Svertilova, *Khim. Geterotsikl. Soedin.* (9), 1252 (1976) [*CA* **86**, 55343 (1977)].

76KG1277 Yu. M. Yutilov and I. A. Svertilova, *Khim. Geterotsikl. Soedin.* (9), 1277 (1976) [*CA* **88**, 22739 (1978)].

76SUP521277 I. A. Svertilova and Yu. M. Yutilov, USSR Pat. 521,277 (1976) [*CA* **85**, 160098w (1976)].

76SUP535908 G. O. P. Doherty, USSR Pat. 535,908 (1976) [*CA* **77**, 16400u (1972)].

76USP3891660 T. Denzel and H. Hoehn, U.S. Pat. 3,891,660 (1976) [*CA* **84**, 4951t (1976)].

76USP3932428 G. O. P. Doherty, U.S. Pat. 3,932,428, (1976) [*CA* **84**, 175157t (1976)].

76USP3961937 G. O. P. Doherty, U.S. Pat. 3,961,937 (1976) [*CA* **85**, 160094s(1976)].

76USP3963734 G. O. P. Doherty and K. H. Fuhr, U.S. Pat. 3,963,734 (1976) [*CA* **85**, 160093r (1976)].

76USP3996233 T. Denzel and H. Hoehn, U.S. Pat. 3,996,233 (1976) [*CA* **85**, 160101s (1976)].

76USP4000145 G. O. P. Doherty, U.S. Pat. 4,000,145 (1976) [*CA* **76**, 85815m (1972)].

76ZN(C)118 M. Roseghini, R. Endean, and A. Temperilli, *Z. Naturforsch (C)*, **31**, 118 (1976).

77AAC114 L. B. Allen, J. H. Huffman, P. D. Cook, R. B. Meyer Jr, R. K. Robins, and R. W. Sidwell, *Antimicrob. Agents Chemother.*, **12**, 114 (1977).

77BRP1465583 CIBA-GEIGY AG, Br. Pat. 1,465,583 (1977) [*CA* **82**, 4256d (1975)].

77BRP1474299 R. K. Robins, R. J. Rousseau and A. M. Mian, Br. Pat. 1,474,299 (1977).

77KG411 G. A. Mokrushina, I. Ya. Postovskiy, and S. K. Kotovskaya, *Khim. Geterotsikl. Soedin.*, 411 (1977) [*CA* **87**, 53170 (1978)].

77KG553 Yu. M. Yutilov and L. I. Kovaleva, *Khim. Geterotsikl. Soedin.*, 553 (1977).

77KG993 Yu. M. Yutilov and A. G. Ignatenko, *Khim. Geterotsikl. Soedin.* (7), 993 (1977) [*CA* **87**, 167943 (1977)].

77PIA(A)204 R. K. Dubey and C. V. Ratnam, *Proc. Indian Acad. Sci. Sect. A*, **85A**, 204 (1977).

77SUP545646 Yu. M. Yutilov and L. I. Kovaleva, USSR Pat. 545,646 (1977).

77SUP557758 W. von Bebenburg, USSR Pat. 557758 (1977) [*CA* **78**, 159,606j (1973)].

77SUP563917 E. Kutter, V. Austel and V. Diederen, USSR Pat. 563,917 (1977) [*CA* **82**, 4251y (1975)].

77SUP566842 Yu. M. Yutilov and L. I. Kovaleva, USSR Pat. 566,842 (1977).

77USP4003908 T. Denzel and H. Hoehn, U.S. Pat. 4,003,908 (1977) [*CA* **86**, 189935y (1977)].

77USP4042593 G. O. P. Doherty, U.S. Pat. 4,042,593 (1977) [*CA* **76**, 85815 m (1972)].

77USP4043182 T. Denzel and H. Hoehn, U.S. Pat. 4,043,182 (1977) [*CA* **86**, 189935y (1977)].

77USP4059584 S. B. Kadin, U.S. Pat. 4,059,584 (1977).

78H113 T. Itoh, K. Ono, and Y. Mizuno, *Heterocycles*, **9**, 113 (1978).

78IJC531 R. K. Dubey and C. V. Ratnam, *Indian J. Chem.*, **16B**, 531 (1978).

78JMC112 R. D. Elliott and J. A. Montgomery, *J. Med. Chem.*, **21**, 112 (1978).

78JMC965 R. L. Clark, A. A. Pessolano, T. -Y. Shen, D. P. Jacobus, H. Jones, V. J. Lotti, and L. M. Flataker, *J. Med. Chem.*, **21**, 965 (1978).

78JOC289 P. D. Cook and R. K. Robins, *J. Org. Chem.*, **43**, 289 (1978).
78MI1 Yu. M. Yutilov and A. G. Ignatenko, Symposium on chemistry and technology of fossil fuel heterocyclic compounds. Abstracts, Donetsk, 73 (1978).
78MI3 Yu. M. Yutilov, O. G. Eilazyan and A. G. Ignatenko, Deposited Doc., VINITI (1978) 129–79
78MI4 H. Foks and M. Janowiec, jykfaifjy, *Acta Pol. Pharm.*, **35** (3), 281 (1978) [*CA* **90**, 168536m (1979)].
78MI5 Yu. M. Yutilov and I. A. Svertilova, Deposited Doc., VINITI (1978)1193–78 [*CA* **91**, 175261 (1979)].
78MI6 Yu. M. Yutilov and I. G. Ignatenko, Deposited Doc., VINITI (1978) 3830–78 [*CA* **92**, 198320 (1980)].
78MI7 Yu. M. Yutilov, A. G. Ignatenko, Deposited Doc., VINITI (1978) 3831–78 [*CA* **92**, 198321 (1980)].
78SUP634673 E. Kutter, F. Austel and V. Diederen, USSR Pat. 634,673 (1978) [*CA* **82**, 4251y (1975)].
78USP4087432 G. O. P. O'Doherty and K. H. Fuhr, U.S. Pat. 4,087,432 (1978) [*CA* **76**, 85815 m (1972)].
78USP4088654 T. Denzel and H. Hoehn, U.S. Pat. 4,088,654 (1978) [*CA* **86**, 189935y (1977)].
79BRP2006758 W. von Bebenburg, K. Thiemer and I. Szeleny, Br. Pat. 2,006,758 (1979) [*CA* **91**, 57010m (1979)].
79CZ387 W. von Bebenburg, G. Steinmetz, and K. Thiele, *Chem. Ztg.*, **103**, 387 (1979).
79IJC428 R. K. Dubey and C. V. Ratnam, *Indian J. Chem.*, **18B**, 428 (1979).
79JHC1063 P. C. Srivastava and R. K. Robins, *J. Heterocycl. Chem.*, **16**, 1063 (1979).
79MI2 Yu. M. Yutilov, K. M. Khabarov and I. A. Svertilova, Deposited Doc., VINITI (1979) 4182–79 [*CA* **94**, 174980a (1981)].
79MI3 R. S. Cahn and O. C. Dermer, Introduction to Chemical Nomenclature, 5th ed., Butterworths, London, Boston (1979).
79SUP667136 D. Arkari, L. Bernardi, D. J. Falkoni, F. Luini, D. J. Palamidessi and U. Skarponi, USSR Pat. 667,136 (1979) [*CA* **87**, 201535y (1977)].
79SUP694511 Yu. M. Yutilov, A. G. Ignatenko and L. E. Michailova, USSR Pat. 694,511 (1979) [*CA* **92**, 163964f (1980)].
79UP1 Yu. M. Yutilov and R. M. Bystrova, unpublished results (1979).
79USP4144341 R. L. Clark, A. A. Pessolano and T. -Y. Shen, U.S. Pat. 4,144,341 (1979) [*CA* **86**, 106592k (1977)].
79USP4148888 G. L. Cantoni, P. K. Chiang and H. H. Richards, U.S. Pat. 4,148,888 (1979) [*CA* **90**, 145597k (1979)].
79USP4152434 B. Schwiesguth, U.S. Pat. 4,152,434 (1979) [*CA* **88**, 50880z, (1978)].
80JHC1757 R. W. Middleton and D. G. Wibberley, *J. Heterocycl. Chem.*, **17**, 1757 (1980).
80IJC863 R. K. Dubey and C. V. Ratnam, *Indian J. Chem.*, **19B**, 863 (1980).
80KG121 Yu. M. Yutilov, A. G. Ignatenko, and O. G. Eilazyan, *Khim. Geterotsikl. Soedin.* (1), 121 (1980) [*CA* **92**, 215357 (1980)].
80OPP234 J. Lee, A. Guthrie, and M. M. Joullie, *Org. Prep. Proced. Int.*, **12** (3–4), 234 (1980).
80SUP717055 Yu. M. Yutilov, A. G. Ignatenko, O. G. Eilazyan and I. A. Svertilova, USSR Pat. 717,055 (1980).
80SUP791241 D. Arkari, L. Bernardi, D. J. Falkoni and U. Skarponi, USSR Pat. 791,241 (1980) [*CA* **91**, 39486s, (1979)].

80USP4195088 F. Barzaghi and M. Bianchi, U.S. Pat. 4,195,088 (1980) [*CA* **90**, 208735i (1979)].
80USP4219559 F. Janssens, R. Stokbroekx, J. Torremans and M. Luyckx, U.S. Pat. 4,219,559 (1980) [*CA* **92**, 215439k (1980)].
81AJC1341 G. B. Barlin and M. D. Fenn, *Aust. J. Chem.*, **34**, 1341 (1981).
81BRP2074858 R. Vinegar and G. Wolberg, G.B. Pat. 2,074,858 (1981) [*CA* **96**, 40937z (1982)].
81GEP3032607 N. H. Itoh, E. H. Sakamoto, M. H. Kawasaki and T. H. Uchida, Ger. Pat. 3,032,607 (1981).
81H1049 H. Inoue, S. Takada, S. Tanigawa, and T. Ueda, *Heterocycles*, **15**, 1049 (1981).
81JA6338 L. Casella and M. Gullotti, *J. Am. Chem. Soc.*, **103**, 6338 (1981).
81KG147 T. D. Miniker and M. N. Preobrazhenskaya, *Khim. Geterotsikl. Soedin.* (2), 147 (1981).
81KG992 Yu. M. Yutilov and O. G. Eilazyan, *Khim. Geterotsikl. Soedin.*, 992 (1981).
81MI1 H. Dugas and C. Penney, in *"Bioorganic Chemistry"* (Ch. R. Cantor ed.), Springer-Verlag, New York, Heidelberg, Berlin (1981).
81MI2 O. G. Eilazyan, and Yu. M. Yutilov, *Reagents and High Pure Substances*, NIITECHIM, Moscow, **3**, 30 (1976).
81MI3 O. Seckin, *Ankara Univ. Eszacilik fakmecmuasi*, **11** (1), 80 (1981).
81MI4 T. Itoh, T. Yamagachi, and Y. Mizuno, *J. Carb.-Nucleos.-Nucl.*, **8**, 119 (1981) [*CA* **95**, 81396v (1981)].
81SUP795478 W. von Bebenburg, I. Szelenyi and K. Thiemer, USSR Pat. 795478 (1981) [*CA* **91**, 57010m (1979)].
81UKZ867 A. V. Stezenko, Yu. P. Kovtun, and S. A. Andrianova, *Ukr. Khim. Zh.*, **47** (8), 867 (1981).
81UP1 O. G. Eilazyan, Yu. M. Yutilov, I. T. Philippov, and I. V. Komissarov, unpublished results (1981).
81USP4247556 W. von Bebenburg, I. Szelenyi and K. Thiemer, U.S. Pat. 4,247,556 (1981) [*CA* **91**, 57010m (1979)].
81USP4276293 G. Y. Lesher, Ch. J. Opalka and D. F. Page, U.S. Pat. 4,276,293 (1981) [*CA* **95**, 2039478z (1981)].
81USP4293696 P. H. L. Wei and S. C. Bell, U.S. Pat. 4,293,696 (1981) [*CA* **96**, 35254v (1982)].
81USP4294836 G. Y. Lesher and R. P. Brundage, U.S. Pat. 4,294,836 (1981) [*CA* **96**, 85551k (1982)].
81USP4294837 G. Y. Lesher, Ch. J. Opalka and D. F. Page, U.S. Pat. 4,294,837 (1981) [*CA* **96**, 85551k (1982)].
82AAC66 D. F. Smee, R. W. Sidwell, S. M. Clark, B. B. Barnett, and R. S. Spendlove, *Antimicrob. Agents Chemother.*, **21**, 66 (1982).
82GEP2118933 S. M. Bloom and H. G. Rogers, Ger. Pat. 2,118,933 (1982).
82GEP3044497 M. Reiffen, Ger. Pat. 3,044,497 (1982) [*CA* **98**, 16710r (1983)].
82JA3162 N. C. Gonnella and J. D. Roberts, *J. Am. Chem. Soc.*, **104**, 3162 (1982).
82H1003 M. Cain, F. Guzman, J. M. Cook, K. C. Rice, and Ph. Skolnick, *Heterocycles*, **19**, 1003 (1982).
82JHC513 T. Itoh, K. Ono, T. Sugawara, and Y. Mizuno, *J. Heterocycl. Chem.*, **19**, 513 (1982).
82JMC1168 J. C. Emmett, G. J. Durant, C. R. Ganellin, A. M. Roe, and J. L. Turner, *J. Med. Chem.*, **25**, 1168 (1982).
82JOC167 N. Katagiri, A. Koshihara, S. Atsuumi, and T. Kato, *J. Org. Chem.*, **47**, 167 (1982).

82KG705 Yu. M. Yutilov and I. A. Svertilova, *Khim. Geterotsikl. Soedin.* (5), 705 (1982) [*CA* **97**, 109950 (1982)].

82MI1 J. L. Medzihradsky, T. P. Zimmerman, G. Wolberg, and G. B. Elion, *J. Immunopharmacol.*, **4**, 29 (1982) [*CA* **98**, 275090h(1983)].

82MI4 D. L. Brutsaert, N. M. De Clerck, P. R. Housmans, and E. R. van Ocken, *J. Cardiovasc. Pharm.*, 333 (1982) [*CA* **97**, 16879g (1982)].

82MI5 Yu. M. Yutilov and O. G. Eilazyan, Deposited Doc., VINITI 1741–83 (1982) [*CA* **101**, 191777v (1984)].

82UP1 Yu. M. Yutilov, O. G. Eilasyan, I. T. Philippov, and I. V. Komissarov, unpublished results (1982).

82USP4309537 G. Y. Lesher, Ch. J. Opalka and D. F. Page, U.S. Pat. 4,309,537 (1982) [*CA* **96**, 85551k (1982)].

82USP4315000 P. D. Cook, U.S. Pat. 4,315,000 (1982) [*CA* **96**, 181576t (1982)].

82USP4317909 G. Y. Lesher and R. P. Brundage, U.S. Pat. 4,317,909 (1982) [*CA* **96**, 85551k (1982)].

82USP4327100 V. Austel, M. Reiffen, J. Heider and W. Diederen, U.S. Pat. 4,327,100 (1982) [*CA* **94**, 208869p (1981)].

82USP4336257 J. J. Baldwin, U.S. Pat. 4,336,257 (1982) [*CA* **95**, 203959d (1981)].

82USP4353909 W. Diederen, A. Prox, A. Reuter, W. Roth and J. Schmid, U.S. Pat. 4,353,909 (1982) [*CA* **97**, 72362v (1982)].

83BRP2113675 W. R. King, Br. Pat. 2,113,675 (1983) [*CA* **97**, 185198q (1982)].

83GEP3132754 R. Jonas, K. Minck, H. -J. Enenkel and H. -J. Schliep, Ger. Pat. 3,132,754 (1983) [*CA* **98**, 198229w (1983)].

83GEP3139064 R. Jonas, K. Minck, H. -J. Enenkel and H. -J. Schliep, Ger. Pat. 3,139,064 (1983) [*CA* **100**, 198229w (1984)].

83GEP3150486 K. Irmscher, O. Saiko, K. -O. Minckand H. -P. Wolf, Ger. Pat. 3,150,486 (1983) [*CA* **100**, 6509c (1984)].

83JHC1015 E. M. Essassi, R. Zniber, A. Bernardini, and Ph. Viallefont, *J. Heterocycl. Chem.*, **20**, 1015 (1983).

83JMC286 A. M. Mian and T. A. Khwaja, *J. Med. Chem.*, **26**, 286 (1983).

83KG1134 Yu. M. Yutilov and O. G. Eilasyan, *Khim. Geterotsikl. Soedin.* (8), 1134 (1983).

83MI1 J. L. Medzihradsky, *Immunopharmacology*, **6**, 51 (1983) [*CA* **99**, 51740t (1983)].

83MI2 H. Dugas and Ch. Penney, in *"Bioorganic Chemistry"* (Ch. R. Cantor ed.), p. 109, Mir, Moscow (1983).

83SUP879944 O. G. Eilazyan, Yu. M. Yutilov and V. I. Orlova, USSR Pat. 879,944 (1983) [*CA* **100**, 19308m (1984)].

83UP1 Yu. M. Yutilov, O. G. Eilazyan, G. V. Kovalev, and I. A. Bocharova, unpublished results (1983).

83USP4387228 J. A. Montgomery and S. D. Clayton, U.S. Pat. 4,387,228 (1983) [*CA* **99**, 105645m (1983)].

83USP4391811 G. Y. Lesher, Ch. J. Opalka and D. F. Page, U.S. Pat. 4,391,811 (1983) [*CA* **99**, 105251e (1983)].

83USP4395552 B. V. Shetty, J. E. Airey and Mt. Kisco, U.S. Pat. 4,395,552 (1983) [*CA* **95**, 203 955z (1981)].

83USP4421755 L. Benedikter and E. Kutter, U.S. Pat. 4,421,755 (1983) [*CA* 98, 95656d (1983)].

84AF1467 G. Arcari, L. Bernardini, R. Cimaschi, G. Falconi, F. Luini, and U. Scarponi, *Arzneim.-Forsch.*, **34**, 1467 (1984).

84CHEC(5) J. A. Montgomery and J. A. Secrist III, in *Comprehensive Heterocyclic Chemistry* (A. R. Katritzky abd Ch. W. Rees, eds.), Vol. 5, pp., 615, 619, 635, 639, Pergamon Press, Oxford, 1984.

84EUP0034038 J. de Witt Overman, Eur. Pat. 0,034,038 (1984).

84EUP0103417 I. C. Pattison, Eur. Pat. 0,103,417 (1984) [*CA* **101**, 28280u (1984)].
84GEP3225386 W. Stenzel, Ger. Pat. 3,225,386 (1984) [*CA* **100**, 209818a (1984)].
84KG132 Yu. M. Yutilov and N. N. Smolyar, *Khim. Geterotsikl. Soedin.* (1), 132 (1984).
84MI1 I. S. Chekman, V. V. Tkachuk, and M. O. Lozinskiy, *Physiologically Active Substances*, **16**, 3 (1984) [*CA* **103**, 53q (1985)].
84MI2 J. L. Medzihradsky, *J. Immunol.*, **133**, 946 (1984) [*CA* **101**, 8859r (1984)].
84USP4447611 D. H. Klaubert and S. C. Bell, U.S. Pat. 4,447,611 (1984) [*CA* **101**, 151845j (1984)].
85GEP3346602 V. Austel, N. Hauel, J. Heider, M. Reiffen, C. A. J. van Meel and W. Diederen, Ger. Pat. 3,346,602 (1985) [*CA* **104**, 19577f (1986)].
85JMC717 D. W. Robertson, E. E. Beedle, J. H. Krushinski, G. Don Pollock, H. Wilson, V. L. Wyss, and J. S. Hayes, *J. Med. Chem.*, **28**, 717 (1985).
85KG1686 Yu. M. Yutilov and N. N. Smolyar, *Khim. Geterotsikl. Soedin.* (12), 1686 (1985).
85MI1 *Drugs of the Future* **10**, 101 (1985).
85MI3 W. R. Leopold, D. W. Fry, T. J. Boritzki, J. A. Besserer, I. C. Pattison, and R. C. Jackson, *Invest. New Drug.*, **3**, 223 (1985) [*CA* **103**, 171581q (1985)].
85MI5 E. Lunt, in *Comprehensive Organic Chemistry* (Russian Translations), (D. Barton and W. D. Ollis, eds.), Vol. 8, pp. 634, 643, Khimiya, Moscow, (1985).
85MI6 D. Kau, J. H. Krushinski, and D. W. Robertson, *J. Labelled Compd. Rad.*, **22**, 1045 (1985) [*CA* **105**, 226439y (1986)].
85MIP379395 D. Binder and F. Rovenszky, Austrian Pat. 379,395 (1985) [*CA* **104**, 19578g (1986)].
86GEP3445299 J. Heider, N. Hauel, V. Austel, J. Van Meel and W. Diederen, Ger. Pat. 3,445,299 (1986) [*CA* **105**, 191085a (1986)].
86JMC138 T. A. Krenitsky, J. L. Rideout, E. Y. Chao, G. W. Koszalka, F. Gurney, R. C. Crouch, N. K. Cohn, G. Wolberg, and R. Vinegar, *J. Med. Chem.*, **29**, 138 (1986).
86KG227 Yu. M. Yutilov and K. M. Khabarov, *Khim. Geterotsikl. Soedin.* (2), 227 (1986).
86KG97 Yu. M. Yutilov and I. A. Svertilova, *Khim. Geterotsikl. Soedin.* (1), 97 (1986).
86MI2 H. Kunze, H. Kleinkauf, and K. Bauer, *Eur. J. Biochem.*, **160**, 605 (1986).
86MRC55 J. C. Lindon, J. M. Williams, and P. Barraclough, *Magn. Reson. Chem.*, **24**, 55 (1986).
86SUP813921 Yu. M. Yutilov, A. G. Ignatenko, L. E. Michailova, E. I. Andreeva and G. V. Bobkova, USSR Pat. 813,921 (1986) [*CA* **106**, 138449s (1987)].
86SUP915432 O. G. Eilazyan, Yu. M. Yutilov, A. G. Ignatenko, V. I. Orlova and V. P. Golubeva, USSR Pat. 915,432, (1986) [*CA* **105**, 92925t (1986)].
86SUP993620 O. G. Eilazyan, Yu. M. Yutilov, V. I. Orlova and V. P. Golubeva, USSR Pat. 993,620 (1986) [*CA* **106**, 156469c (1987)].
86SUP1039174 O. G. Eilazyan, Yu. M. Yutilov and P. N. Steblyuk, USSR Pat. 1,039,174 (1986) [*CA* **106**, 213 947h (1987)].
86SUP1047148 Yu. M. Yutilov, A. G. Ignatenko, L. E. Michailova, V. V. Kirichenko and L. P. Orestenko, USSR Pat. 1,047,148 (1986) [*CA* **107**, 39818a (1987)].
86SUP1048742 Yu. M. Yutilov, A. G. Ignatenko, L. E. Michailova and V. V. Kirichenko, USSR Pat. 1,048,742 (1986).

86SUP1048743 Yu. M. Yutilov, A. G. Ignatenko, L. E. Michailova and V.V. Kirichenko, USSR Pat. 1,048,743 (1986).

86SUP1048744 Yu. M. Yutilov, A. G. Ignatenko and L. E. Michailova, USSR Pat. 1,048,744 (1986).

86T1511 A. Frankowski, *Tetrahedron*, **42**, 1511 (1986).

86TL5997 P. Barraclough, R. Iyer, J. C. Lindon, and J. M. Williams, *Tetrahedron Lett.*, **27**, 5997 (1986).

86ZOR445 Yu. M. Yutilov, L. E. Michailova, and A. G. Ignatenko, *Zh. Org. Khim.*, **22** (2), 445 (1986).

86ZOR1793 Yu. M. Yutilov and N. N. Smolyar, *Zh. Org. Khim*, **22** (8), 1793 (1986).

87AX(C)1937 P. Luger, E. Robins, E. Kutter, and V. Austel, *Acta Crystallogr. Sect. C*, **43**, 1937 (1987).

87JFC581 S. Fujii, Y. Maki, H. Kimoto, and L. A. Cohen, *J. Fluorine Chem.*, **35**, 581 (1987).

87JMC1746 C. Temple Jr., J. D. Rose, R. N. Comber, and G. A. Rener, *J. Med. Chem.*, **30**, 1746 (1987).

87KG639 Yu. M. Yutilov and L. I. Shcherbina, *Khim. Geterotsikl. Soedin.* (5), 639 (1987).

87KG995 Yu. M. Yutilov and A. G. Ignatenko, *Khim. Geterotsikl. Soedin.* (7), 995 (1987).

87MI1 Y. N. Han, S. Y. Ryu, B. H. Han, and L. K. Woo, *Arch. Pharm. Res.*, **10**, 258 (1987) [*CA* **108**, 36397x (1988)].

87MI4 S. Ichida, S. Ariyoshi, T. Tanaka, K. Sobue, Y. Okazaki, and K. Yoshioka, *Jpn. J. Pharmacol.*, **45**, 187 (1987) [*CA* **108**, 35423r (1988)].

87SUP991716 K. M. Khabarov, Yu. M. Yutilov, I. T. Philippov and I. V. Komissarov, USSR Pat. 991,716 (1987) [*CA* **109**, 48452v (1988)].

87SUP1048746 Yu. M. Yutilov, K. M. Khabarov, I. V. Komissarov and I. T. Philippov, USSR Pat. 1,048,746 (1987) [*CA* **109**, 48453w (1988)].

87SUP1094303 K. M. Khabarov, Yu. M. Yutilov, I. T. Philippov, I. V. Komissarov and I. A. Svertilova, USSR Pat. 1,094,303 (1987) [*CA* **109**, 86344u (1988)].

88EUP260613 P. W. Manley, R. A. Porter, Eur. Pat. 260,613 (1988) [*CA* **109**, 73438c (1988)].

88H2423 E. Davioud, J. -Ch. Quirion, M. E. Tale, J. Tempe, and H. -Ph. Husson, *Heterocycles*, **27**, 2423 (1988).

88JHC1255 J. L. Kelley, J. A. Linn, J. L. Rideout, and F. E. Soroko, *J. Heterocycl. Chem.*, **25**, 1255 (1988).

88KFZ20 I. K. Boreisha, A. T. Dolzhenko, S. I. Komissarov, Yu. M. Yutilov, O. G. Eilazyan and T. V. Khabarova, *Khim. Farm. Zh.*, **22**, 20 (1988).

88KG799 Yu. M. Yutilov and I. A. Svertilova, *Khim. Geterotsikl. Soedin.* (6), 799 (1988).

88MI3 P. Restani, P. Campagner, A. Fiecchi, P. Resmini, and C. L. Galli, *Food Chem. Toxicol.*, **26**, 441 (1988) [*CA* **109**, 127482 h (1988)].

88SUP851940 O. G. Eilazyan, K. M. Khabarov, Yu. M. Yutilov and P. N. Steblyuk, USSR Pat. 851,940 (1988).

89CCC1096 M. M. Girges, M. M. A. El-Zahab, and M. A. Hanna, *Collect. Czech. Chem. Commun.*, **54**, 1096 (1989).

89JHC289 P. Savarino, G. Viscardi, R. Carpignano, A. Borda, and E. Barni, *J. Heterocycl. Chem.*, **26**, 289 (1989).

89JHC1819 A. H. M. Al-Shaar, D. W. Gilmour, D. J. Lythgoe, I. McClenaghan, and Ch. A. Ramsden, *J. Heterocycl. Chem.*, **26**, 1819 (1989).

89KFZ56 Yu. M. Yutilov, O. G. Eilazyan, T. V. Khabarova, E. I. Boreko, G. V. Vladiko, and L. V. Korobchenko, *Khim. Farm. Zh.*, **23**, 56 (1989).

89KFZ160 Yu. M. Yutilov, O. G. Eilazyan, L. I. Shcherbina, G. V. Kovalev, I. N. Tyurenkov, and G. V. Streltzova, *Khim. Farm. Zh.*, **23**, 160 (1989).

89KFZ697 Yu. M. Yutilov, A. G. Ignatenko, B. E. Afanasiev, V. V. Kirichenko, L. P. Orestenko, and V. I. Linenko, *Khim. Farm. Zh.*, **23**, 697 (1989).

89KG940 Yu. M. Yutilov, L. I. Shcherbina, and A. F. Efremenko, *Khim. Geterotsikl. Soedin.* (7), 940 (1989).

89MI1 C. L. Galli, P. Allevi, D. Colombo, E. Corsini, P. Marinelli, L. Orlando, and P. Restani, *Food Chem. Toxicol.*, **27**, 651 (1989) [*CA* **112**, 156900k (1990)].

89PHA267 L. Bukowski and M. Janowiec, *Pharmazie*, **44**, 267 (1989).

89UP1 Yu. M. Yutilov, unpublished results (1989).

89USP4804658 P. W. Manley and R. A. Porter, U.S. Pat. 4,804,658 (1989).

90AP501 P. Barraclough, J. W. Black, D. Cambridge, V. P. Gerscowitch, R. A. D. Hull, R. Lyer, W. R. King, C. O. Kneen, M. S. Nobbs, G. Shah, S. Smith, S. J. Vine, and M. V. Whiting, *Arch. Pharm.,* (Weinheim, Ger.), **323**, 501 (1990).

90JHC531 R. Lis, J. A. Traina, and J. C. Huffman, *J. Heterocycl. Chem.*, **27**, 531 (1990).

90JHC563 A. S. Katner and R. F. Brown, *J. Heterocycl. Chem.*, **27**, 563 (1990).

90JHC1777 P. Savarino, G. Viscardi, E. Barni, and R. Carpignano, *J. Heterocycl. Chem.*, **27**, 1777 (1990).

90JHC1821 J. L. Kelley, Ed. W. McLean, R. G. Davis, and R. Crouch, *J. Heterocycl. Chem.*, **27**, 1821 (1990).

90JHC1825 G. Viscardi, P. Savarino, E. Barni, and R. Carpignano, *J. Heterocycl. Chem.*, **27**, 1825 (1990).

90MI1 L. Kaczmarek, P. Nantka-Namirski, E. Moryl, and E. Chojnacka-Wojcik, *Pol. J. Pharmacol. Pharm.*, **42**, 79 (1990) [*CA* **114**, 114909f (1991)].

90MI3 D. T. Dudley, R. L. Panek, T. C. Major, G. H. Lu, R. F. Bruns, B. A. Klinkefus, J. C. Hodges, and R. E. Weishaar, *Mol. Pharmacol.*, **38**, 370 (1990) [*CA* **113**, 225090f (1990)].

90MI4 M. V. Yure, E. Yu. Gudriniece, M. V. Petrova, E. K. Rancane, and I. B. Mazeika, *Izv. Akad. Nauk Latv. SSR, Ser. Khim.* (4), 439 (1990).

90USP4904785 D. W. Robertson and J. S. Hayers, U.S. Pat. 4,904,785 (1990) [*CA* **100**, 103347f (1984)].

91JHC97 S. Klutchko, J. C. Hodges, C. J. Blankley, and N. L. Colbry, *J. Heterocycl. Chem.*, **28**, 97 (1991).

91JMC2919 N. B. Mantlo, P. K. Chakravarty, D. L. Ondeyka, P. K. S. Siegl, R. S. Chang, V. J. Lotti, K. A. Faust, T. -B. Chen, T. W. Schorn, Ch. S. Sweet, S. E. Emmert, A. A. Patchett, and W. J. Greenlee, *J. Med. Chem.*, **34**, 2919 (1991).

91JMC2993 B. E. Tomczuk, C. R. Taylor, L. M. Moses, D. B. Sutherland, Y. S. Lo, D. N. Johnson, W. B. Kinnier, and B. F. Kilpatrick, *J. Med. Chem.*, **34**, 2993 (1991).

91JMC3248 C. J. Blankley, J. C. Hodges, S. R. Klutchko, R. J. Himmelsbach, A. Chucholowski, C. J. Connolly, S. J. Neergaard, M. S. Van Nieuwenhze, A. Sebastian, J. Quin, A. D. Essenburg, and D. M. Cohen, *J. Med. Chem.*, **34**, 3248 (1991).

91MI1 V. L. Rusinov and O. N. Chupakhin, *Nitroazines*, Nauka, Novosybyrsk, (1991).
91MI2 T. H. Gieske, N. S. Doherty, R. Raddatz, and D. Stephens, *Pharmacology*, **42**, 151 (1991) [*CA* **114**, 99128c (1991)].
91TL6503 D. L. Bussolotti, J. L. LaMattina, and K. James, *Tetrahedron Lett.*, **32**, 6503 (1991).
91TL6915 T. Kuroda and F. Suzuki, *Tetrahedron Lett.*, **32**, 6915 (1991).
91USP4988707 M. A. Stealey and G. D. Searle & Co, U.S. Pat. 4,988,707 (1991) [*CA* **109**, 93048d (1988)].
91USP5019581 I. K. Khanna, R. Nosal, R. Weier, G. D. Searle & Co, U.S. Pat. 5,019,581 (1991) [*CA* **112**, 235299z (1990)].
91USP5053329 Sh. -Sh. T. Chen and B. H. Arison, U.S. Pat. 5,053,329 (1991) [*CA* **116**, 57535w (1992)].
91USP5066654 Ch. R. Taylor and M. Moses, U.S. Pat. 5,066,654 (1991) [*CA* **117**, 48553u, (1992)].
91ZOR1120 Yu. M. Yutilov and N. N. Smolyar, *Zh. Org. Khim.*, **27** (5), 1120 (1991).
92FES287 M. Loriga, G. Paglietti, S. Piras, F. Sparatore, V. Anania, M. P. Demontis, M. V. Varoni, and M. C. Fattaccio, *Farmaco Ed. Sci.*, **47**, 287 (1992).
92MI1 P. Restani, A. R. Restelli, and C. L. Galli, *Food Addit. Contam.*, **9**, 597 (1992).
92MIP4025358 U. Ries, B. Narr, A. Bomhard, N. Haueb, J. Van Meel, W.Wienen, and M. Entzeroth, Application for Ger. Pat. 4,025,358 (1992) [*CA* **117**, 26560s (1992)].
92UP1 Yu. M. Yutilov, unpublished results (1992).
92USP5081253 A. A. Santilli, a. c. Scotese, and d. P. Strike, U.S. Pat. 5,081,253 (1992) [*CA* **115**, 136098p (1991)].
93CCC1419 H. Dvorakova and A. Holy, *Collect. Czech. Chem. Commun.*, **58**, 1419 (1993).
93JHC37 G. -H. Kuo, E. R. Bacon, B. Singh, M. A. Eissenstat, and G. Y. Lesher, *J. Heterocycl. Chem.*, **30**, 37 (1993).
93JOC7952 T. Choshi, A. Tonari, H. Yoshioka, K. Harada, E. Sugino, and S. Hibino, *J. Org. Chem.*, **58**, 7952 (1993).
93ZOR2035 A. N. Frolov and N. I. Rtishchev, *Zh. Org. Khim.*, **29** (10), 2035 (1993).
94FES345 A. Chimirri, S. Grasso, A. M. Monforte, P. Monforte, and M. Zappala, *Farmaco, Ed. Sci.*, **49**, 345 (1994).
94H529 S. Lindström, T. Ahmad, and S. Grivas, *Heterocycles*, **38**, 529 (1994).
94H1527 Y. Blache, A. Gueiffier, O. Chavignon, H. Viols, J. C. Teulade, and J. P. Chapat, *Heterocycles*, **38**, 1527 (1994).
94HCA1057 J. Sraga, Ph. Guerry, and I. Kompis, *Helv. Chim. Acta*, **77**, 1057 (1994).
94HCA2175 S. Schwoch, W. Kramer, R. Neidlein, and H. Suschitzky, *Helv. Chim. Acta*, **77**, 2175 (1994).
94JCR(S)268 S. Grivas and E. Ronne, *J. Chem. Res. (S)*, **7**, 268 (1994).
94JCR(S)426 P. Barraclough, S. Smith, J. M. Gillam, D. Kettle, and M. S. Nobbs, *J. Chem. Res. (S)*, **11**, 426 (1994).
94JHC73 E. Nicolai, S. Claude, and J. M. Teulon, *J. Heterocycl. Chem.*, **31**, 73 (1994).
94JHC453 R. K. Gautam, S. Fujii, M. Nishida, and H. Kimoto, *J. Heterocycl. Chem.*, **31**, 453 (1994).
94JHC1641 M. J. Tanga, J. E. Bupp, and T. K. Tochimoto, *J. Heterocycl. Chem.*, **31**, 1641 (1994).

94JMC248 B. Singh, E. R. Bacon, S. Robinson, R. K. Fritz, G. Y. Lesher, V. Kumar, J. A. Dority, M. Reuman, G. -H. Kuo, M. A. Eissenstat, E. D. Pagani, D. C. Bode, R. G. Bentley, M. J. Connell, L. T. Hamel, and P. J. Silver, *J. Med. Chem.*, **37**, 248 (1994).

94JMC305 G. C. B. Harriman, E. Abushanab, and J. D. Stoeckler, *J. Med. Chem.*, **37**, 305 (1994).

94JMC1632 W. W. K. R. Mederski, D. Dorsch, H. -H. Bokel, N. Beier, I. Lues, and P. Schelling, *J. Med. Chem.*, **37**, 1632 (1994).

94KFZ58 Yu. M. Yutilov, I. N. Tyurenkov, N. N. Smolyar, T. M. Panchenko, and V. V. Kovtun, *Khim. Farm. Zh.*, **28**, 58 (1994).

94KG1071 Yu. M. Yutilov and I. A. Svertilova, *Khim. Geterotsikl. Soedin.* (8), 1071 (1994).

94KG1076 Yu. M. Yutilov and I. A. Svertilova, *Khim. Geterotsikl. Soedin.* (8), 1076 (1994).

94KG1232 Yu. M. Yutilov and A. G. Ignatenko, *Khim. Geterotsikl. Soedin.* (9), 1232 (1994).

94MI1 N. B. Mantlo, D. Kim, D. Ondeyka, R. S. L. Chang, S. D. Kivlighn, P. K. S. Siegl, and W. J. Greenlee, *Bioorg. Med. Chem. Lett.*, **4**, 17 (1994).

94MI2 N. Cho, K. Kubo, S. Furuya, Y. Sagiura, T. Yasuma, Y. Kohara, M. Ojima, Y. Inada, K. Nishikawa, and T. Naka, *Bioorg. Med. Chem. Lett.*, **4**, 35 (1994).

94MI3 P. A. Carpino, S. F. Sneddon, P. Da Silva Jardine, G. T. Magnus-Ayritey, A. L. Rauch, and M. R. Burkard, *Bioorg. Med. Chem. Lett.*, **4**, 93 (1994).

94MI4 R. T. Wester, C. J. Mularski, G. T. Magnus-Ayritey, P. Da Silva Jardine, J. A. LaFlamme, H. Berke, D. L. Bussolotti, A. L. Rauch, K. W. Hoover, Ch. A. Kennedy, M. R. Burkard, M. L. Mangiapane, Ch. E. Aldinger, K. Cooper, and P. A. Carpino, *Bioorg. Med. Chem. Lett.*, **4**, 133 (1994) [*CA* **121**, 458x (1994)].

94MI5 E. Klauschenz, V. Hagen, B. Wiesner, A. Hagen, G. Reck, and E. G. Krause, *Eur. J. Med. Chem.*, **29**, 175 (1994) [*CA* **121**, 57294v (1994)].

94MI7 S. J. McGarry and A. J. Williams, *Br. J. Pharmacol.*, **111**, 1212 (1994).

94SC1363 E. Ronne, K. Olsson, and S. Grivas, *Synth. Commun.*, **24**, 1363 (1994).

94TL5775 C. H. Senanayake, L. E. Fredenburgh, R. A. Reamer, J. Liu, R. D. Larsen, T. R. Verhoeven, and P. J. Reider, *Tetrahedron Lett.*, **35**, 5775 (1994).

94ZOR429 Yu. M. Yutilov, L. I. Shcherbina, and N. N. Smolyar, *Zh. Org. Khim.*, **30** (3), 429 (1994).

94ZOR440 Yu. M. Yutilov and N. N. Smolyar, *Zh. Org. Khim.*, **30** (3), 440 (1994).

94ZOR460 Yu. M. Yutilov, L. I. Shcherbina, and L. V. Stezenko, *Zh. Org. Khim.*, **30** (3), 460 (1994).

95ACSA361 S. Lindström, *Acta Chem. Scand.*, **49**, 361 (1995).

95H161 H. Yashioka, T. Choshi, E. Sugino, and S. Hibino, *Heterocycles*, **41**, 161 (1995).

95JHC467 S. Grivas and S. Lindstrom, *J. Heterocycl. Chem.*, **32**, 467 (1995).

95JMC3524 M. J. Fray, D. J. Bull, K. Cooper, M. J. Parry, and M. H. Stefaniak, *J. Med. Chem.*, **38**, 3524 (1995).

95JOC960 I. K. Khanna, R. M. Weier, K. T. Lentz, L. Swenton, and D. C. Lankin, *J. Org. Chem.*, **60**, 960 (1995).

95JOC5243 J. B. Campbell and J. W. Firor, *J. Org. Chem.*, **60**, 5243 (1995).
95JOU1429 Yu. M. Yutilov, M. G. Abramyants, and N. N. Smolyar, *J. Org. Chem. USSR (Engl. Transl.)*, **31** (10), 1429 (1995).
95MI1 Y. S. Tuininga, D. J. van Veldhuisen, H. J. Crijns, S. A. van den Broek, J. Brouwer, J. Haaksma, A. J. Man in 't Veld, and K. I. Lie, *J. Cardiovasc. Pharmacol.*, **25**, 81 (1995) [*CA* **122**, 46139t (1995)].
95MI3 Yu. M. Yutilov, N. N. Smolyar, S. V. Gresko, and L. I. Shcherbina, XVII Ukrainian Conference on Organic Chemistry, Abstracts, Kharkov, 1995, p. 92.
95MI4 P. G. Borasio, B. Pavan, E. Fabbri, F. Ginanni-Corradini, D. Arcelli, and A. Poli, *Neurosci. Lett.*, **184**, 97 (1995) [*CA* **122**, 97062v (1995)].
95MI6 E. J. Kelso, B. J. McDermott, and B. Silke, *Biochem. Pharmacol.*, **49**, 441 (1995) [*CA* **122**, 178053 (1995)].
95MI7 C. De Mey, *Br. J. Clin. Pharmacol.*, **39**, 485 (1995) [*CA* **123**, 47263m (1995)].
95MI8 J. E. Macor, D. H. Blank, K. Desai, C. B. Fox, B. K. Koe, L. A. Lebel, R. J. Post, A. W. Schmidt, D. W. Schulz, and P. A. Seymour, *Bioorg. Med. Chem. Lett.*, **5** (20), 2391 (1995) [*CA* **124**, 86957f (1996)].
95TL1601 T. A. Devlin, E. Lacrosaz-Rouanet, D. Vo, and D. J. Jebaratnam, *Tetrahedron Lett.*, **36**, 1601 (1995).
95UP Yu. M. Yutilov and L. V. Stezenko, unpublished results (1995).
95ZOR304 Yu. M. Yutilov, N. N. Smolyar, and S. V. Gresko, *Zh. Org. Khim.*, **31**, 304 (1995).
95ZOR1577 Yu. M. Yutilov, M. G. Abramyantz, and N. N. Smolyar, *Zh. Org. Khim.*, **31**, 1577 (1995).
96AX(C)1019 W. Shin, T. -S. Yoon, and S. E. Yoo, Acta Crystallogr., *Sect. C*, **52**, 1019 (1996).
96HCA169 T. Wenzel and F. Seela, *Helv. Chim. Acta*, **79**, 169 (1996).
96JOU564 Yu. M. Yutilov and L. I. Shcherbina, *J. Org. Chem. USSR (Engl. Transl.)*, **32**, 564 (1996).
96MI1 L. Pellegrino and P. Resmini, *Z. Lebensm. Unters. Forsch.*, **202**, 66 (1996) [*CA* **125**, 56706b (1996)].
96MI2 R. Bossa, M. Bissoli, M. Chiericozzi, R. Cozzi, I. Galatulas, and G. Salvatore, *Anticancer Res*, **16**, 141 (1996) [*CA* **125**, 507v (1996)].
96MI3 K. Hata, Y. Goto, S. Futaki, T. Takasago, A. Saeki, T. Nishioka, and H. Suga, *J. Card. Fail.*, 203 (1996).
96UKZ64 I. A. Svertilova, N. N. Smolyar, and Yu. M. Yutilov, *Ukr. Khim. Zh.*, **62** (3–4), 64 (1996).
96ZOR586 Yu. M. Yutilov and L. I. Shcherbina, *Zh. Org. Khim.*, **32**, 586 (1996).
97MI1 M. Van der Ent, W. J. Remme, G. L. Bartels, P. W. De Leeuw, D. C. Van Hoogenhuyze, and D. A. Kruijssen, *J. Card. Fail.*, **3**, 277 (1997) [*CA* **127**, 206406u (1997)].
97MI2 D. H. Svendsrud, T. Loennechen, and J. O. Winberg, *Biochem. Pharmacol.*, **53**, 1511 (1997) [*CA* **127**, 199640c (1999)].
97SUP921235 Yu. M. Yutilov and A.F. Efremenko, USSR Pat. 921,235 (1997).
97SUP1010846 Yu. M. Yutilov, I. V. Komissarov, K. M. Khabarov and I. T. Philippov, USSR Pat. 1,010,846 (1997).
97SUP1048745 Yu. M. Yutilov, K. M. Khabarov, L. P. Orestenko and V. V. Kirichenko, USSR Pat. 1,048,745 (1997).
97SUP1067801 O. G. Eilazyan, Yu. M. Yutilov, I. T. Philippov and I. V. Komissarov, USSR Pat. 1,067,801 (1997).

97SUP1220307 Yu. M. Yutilov, O. G. Eilazyan, I. V. Komissarov, A. T. Dolzhenko, I. I. Abramets and S. I. Komissarov, USSR Pat. 1,220,307 (1997).

97SUP1262927 Yu. M. Yutilov, L. N. Manshilina, A. V. Kazimov, A. A. Akova, K. M. Kirillova, I. A. Svertilova and L. V. Minkina, USSR Pat. 1,262,927 (1997).

97SUP1282506 Yu. M. Yutilov, L. I. Shcherbina, I. T. Philippov, I. V. Komissarov, S. E. Serdyuk, USSR Pat. 1,282,506 (1997).

97SUP1387375 O. G. Eilazyan, Yu. M. Yutilov, I. T. Philippov and I. V. Komissarov, USSR Pat. 1,387,375 (1997).

97UP1 Yu. M. Yutilov and I. A. Svertilova, unpublished results (1997).

98JMC74 M. L. Curtin, S. K. Davidsen, H. R. Heyman, R. B. Garland, G. S. Sheppard, A. S. Florjancic, L. Xu, G. M. Carrera, D. H. Steinman, J. A. Trautmann, D. H. Albert, T. J. Magoc, P. Tapang, D. A. Rhein, R. G. Conway, G. Luo, J. F. Denissen, K. C. Marsh, D. W. Morgan, and J. B. Summers, *J. Med. Chem.*, **41**, 74 (1998).

98MI1 Yu. M. Yutilov, I. N. Tyurenkov, O. G. Eilazyan, M. G. Abramiantz, G. V. Streltzova, N. N. Smolyar, L. I. Shcherbina, and T. V. Khabarova in Papers on Scientific Conference NAS of Ukraine "Scientific development of drugs", Osnova, Kharkov, 1998, p. 264.

98MI2 Yu. M. Yutilov, N. N. Smolyar, I. N. Tyurenkov, and N. V. Timko in Papers on XVIII Ukrainian Scientific Conference on Organic Chemistry, Dnepropetrovsk, 1998, p. 390.

98SUP879945 L. I. Shcherbina, Yu. M. Yutilov and L. V. Zhivova, USSR Pat. 879,945 (1998).

98SUP879946 A. G. Ignatenko, Yu. M. Yutilov, L. E. Michailova and V. V. Verbitskaya, USSR Pat. 879,946 (1998).

98UP1 Yu. M. Yutilov and A. G. Ignatenko, unpublished results (1998).

98UP2 Yu. M. Yutilov, A. G. Ignatenko, and L. E. Michailova, unpublished results (1998).

98ZOR1420 Yu. M. Yutilov, V. F. Malyutina, Ch. Ya. Lopatinskaya, and I. A. Svertilova, *Zh. Org. Khim.*, **34** (9), 1420 (1998).

99JOU583 Yu. M. Yutilov and I. A. Svertilova, *Russian J. Org. Chem. USSR (Engl. Transl.)*, **35**, 583 (1999).

99MI1 W. W. Woltersdorf, A. Bowron, A. P. Day, J. Scott, and D. Stansbie, *Ann. Clin. Biochem.*, **36** (Pt 4), 533 (1999) [*CA* **132**, 90283r (2000)].

99MI2 L. Wong, R. Aarhus, H. C. Lee, and T. F. Walseth, *Biochim. Biophys. Acta*, **1472**, 555 (1999) [*CA* **132**, 73235j (2000)].

99MI3 G. Walker, A. C. Langheinrich, E. Dennhauser, R. M. Bohle, T. Dreyer, J. Kreuzer, H. Tillmanns, R. C. Braun-Dullaeus, and W. Haberbosch, *Arterioscler. Thromb. Vasc. Biol.*, **19**, 2673 (1999) [*CA* **132**, 231708x (2000)].

99UP2 Yu. M. Yutilov and N. N. Smolyar, unpublished results (1999).

99ZOR474 Yu. M. Yutilov and I. A. Svertilova, *Zh. Org. Khim.*, **35** (3), 474 (1999).

99ZOR608 Yu. M. Yutilov and I. A. Svertilova, *Zh. Org. Khim.*, **35** (4), 608 (1999).

2000MI1 Yu. M. Yutilov, N. N. Smolyar, S. V. Gresko, and A. V. Eresko, "The first All-Russian Conference on Heterocyclic Chemistry named after A.N. Kost, Suzdal, 2000, p. 50.

2001KFZ16 Yu. M. Yutilov, N. N. Smolyar, M. G. Abramyantz, and I. N. Tyurenkov, *Khim. Farm. Zh.*, **35** (1), 16 (2001).

2001UKZ111 Yu. M. Yutilov and N. N. Smolyar, *Ukr. Khim. Zh.*, **67**, 111 (2001).

2001ZOR129 Yu. M. Yutilov, M. G. Abramyantz, and N. N. Smolyar, *Zh. Org. Khim.*, **37** (1), 129 (2001).

2001ZOR1076 S. V. Gresko, N. N. Smolyar, and Yu. M. Yutilov, *Zh. Org. Khim.*, **37** (7), 1076 (2001).

2002ZOR440 Yu. M. Yutilov, N. N. Smolyar, and N. V. Astashkina, *Zh. Org. Khim.*, **38** (3), 440 (2002).

2003ZOR302 Yu. M. Yutilov, K. Y. Lopatinskaya, N. N. Smolyar, and I. V. Korol, *Zh. Org. Khim.*, **39** (2), 302 (2003).

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